Health Evidence Review Commission's Value-based Benefits Subcommittee

November 12, 2015

8:00 AM

Clackamas Community College
Wilsonville Training Center, Room 111-112
29373 SW Town Center Loop E, Wilsonville, Oregon, 97070

Section 1.0

Call to Order

AGENDA
VALUE-BASED BENEFITS SUBCOMMITTEE
November 12, 2015
8:00am - 1:00pm
Clackamas Community College
Wilsonville Training Center, Rooms 111-112
Wilsonville, Oregon
A working lunch will be served at approximately 12:00 PM
All times are approximate

I. Call to Order, Roll Call, Approval of Minutes – Kevin Olson **8:00 AM**

II. Staff report – Ariel Smits, Cat Livingston, Darren Coffman **8:05 AM**

A. Errata
B. Back line change delay

III. Straightforward/Consent agenda – Ariel Smits **8:10 AM**

A. Straightforward table
B. Straightforward back lines corrections
C. Peripheral vascular disease line revisions

IV. 2016 CPT/HCPCS code review – Ariel Smits **8:15 AM**
AM

A. Consent agenda
   A. Straightforward/consent 2016 CPT code spreadsheet
   B. Paravertebral nerve blocks

B. Codes requiring discussion
   A. Endobronchial ultrasound (EBUS)
   B. Sclerotherapy for cysts/seromas
   C. Ureteral embolization or occlusion
   D. Intra-arterial interventions for acute stroke
   E. Intracranial intravascular infusion other than thrombotics
   F. Fetal MRI follow up
   G. Gastric emptying with small bowel/colon transit
   H. Genetic testing codes
      1. Non-prenatal genetic testing guideline
      2. Prenatal genetic testing guideline
   I. Tumor marker codes
   J. Genetic tests for disease management
   K. Vestibular tests
   L. Arterial pressure waveform analysis
   M. Photoscreening

C. 2016 HCPCS codes

V.	**New discussion items – Ariel Smits** **A.** Adjustment disorder coding specification **B.** Thromboangiitis obliterans	**10:30 AM**
VI.	**Guidelines – Ariel Smits, Cat Livingston** **A.** Acupuncture **B.** Tobacco cessation coverage and prevention **C.** Tobacco use and elective surgery	**10:50 AM**
VII.	**Coverage Guidances for review – Cat Livingston** **A.** Planned out-of-hospital births **B.** Indications for proton beam therapy	**11:30 PM**
VIII.	**Public comment**	**12:55 PM**
IX.	**Adjournment – Kevin Olson**	**1:00 PM**

Value-based Benefits Subcommittee Recommendations Summary
For Presentation to:
Health Evidence Review Commission on October 1, 2015 (Revised)

For specific coding recommendations and guideline wording, please see the text of the 10-1-2015 VbBS minutes.

RECOMMENDED CODE MOVEMENT (effective 1/1/16)

- Remove the procedure codes for temporary prostatic stents from 2 covered lines and place on the Services Recommended for Non-Coverage Table as investigational
- Add the 2016 CDT codes to various dental lines as recommended by the Oral Health Advisory Panel
- Add the procedure code for silver diamine fluoride application to the covered dental caries line
- Delete the procedure code for vertebral fracture assessment using DXA from the Diagnostic File and add to the Services Recommended for Non-Coverage Table as investigational
- Add several ophthalmology visit and evaluation codes to the Diagnostic File to allow for the evaluation of urgent eye conditions
- Add procedure codes to a covered line to allow trochanteric bursitis to be treated with steroid injections
- Clarify placement of various procedures and diagnoses relating to nose deformities. The repair of the tip of the nose not involved with cleft palate was moved to the Services Recommended for Non-Coverage Table.
- Add procedure codes for stem cell transplant to the covered line containing neuroblastoma with a new guideline limiting use to high-risk neuroblastoma
- Move all child abuse and neglect diagnosis codes to a single covered line, which had all mental health service procedure codes also added to it
- Add diagnosis and procedure codes for repair of ear drum perforations to the two covered hearing loss lines with a guideline
- Add and delete codes related to various straightforward changes
- Add procedure codes for breast augmentation to the covered gender dysphoria line; remove procedure codes for penile implants from this line

ITEMS CONSIDERED BUT NO RECOMMENDATIONS FOR CHANGES MADE

- Optic neuritis did not have its prioritization changed from its current non-covered line

RECOMMENDED GUIDELINE CHANGES (effective 1/1/16)

- Add a new guideline governing the use of silver diamine fluoride for use only with dental caries up to twice a year
- Delete the existing guideline indicating lack of coverage for silver compounds for dental
- Add a new guideline outlining when ophthalmology codes are considered diagnostic

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- Add a new guideline to clarify when trochanteric bursitis is included on a covered line (for steroid injections and physical therapy) and when it is included on a non-covered line (for surgical procedures)
- Modify the guideline for nose tip repair in cleft palate to clarify when this procedure is covered
- Delete the guideline regarding reconstruction of the nose
- Add new guidelines limiting the use of botulinum toxin injections for the treatment of migraines and bladder conditions.
- Modify the time period allowed for repair of peripheral nerve injuries from 8 weeks to 6 months in the nerve injury guideline
- Delete the statement of intent about behavioral and physical health integration
- Modify the ADHD guideline to clarify coverage
- Delete 3 mental health guidelines for children as no longer necessary
- Modify the gender dysphoria guideline to specify when breast augmentation is covered

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MINUTES (REVISED)

VALUE-BASED BENEFITS SUBCOMMITTEE
Clackamas Community College
Wilsonville Training Center, Rooms 111-112
Wilsonville, Oregon
October 1, 2015
8:30 AM – 1:00 PM

Members Present: Kevin Olson, MD, Chair; David Pollack, MD; Susan Williams, MD; Mark Gibson; Irene Croswell, RPh; Holly Jo Hodges, MD; Laura Ocker, LAc.

Members Absent: none

Staff Present: Darren Coffman; Ariel Smits, MD, MPH; Cat Livingston, MD, MPH; Jason Gingerich; Denise Taray, RN; Daphne Peck (by phone).

Also Attending: Jesse Little, Kim Wentz, MD, MPH (by phone), Bruce Austin, DMD, and Brian Nieubuurt (Oregon Health Authority); Megan Bird, MD (Legacy Health); Karen Campbell and Jane Stephen (Allergan); Katie Noah (Willamette Dental); Jeanne Stagner (Klamath's Women's Center); Amy Rainbow (Birth Network National); Courtney Johnson (COHO); Karen Nolon (ODS); Neola Young and Emily McCan (Basic Rights Oregon); Amy Penkin, LSCW and Erica Pettigrew, MD (OHSU); Carl Stevens (Care Oregon); Pau Nielsen (Allermes); Sharron Fuchs; Carole Levana; Duncan Nielsen, MD; Pam Keuncke (PHS); Silke Akerson (Oregon Midwifery Council).

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- **Roll Call/Minutes Approval/Staff Report**

  The meeting was called to order at 8:45 am and roll was called. Minutes from the August, 2015 VbBS meeting were reviewed and approved.

  Staff reported that ICD-10-CM has been implemented as of today. All ICD-9 placement recommendations in the October VbBS packet are now informational only. HERC staff will keep ICD-9 codes available on and alternate version of the Prioritized List for the next few months for informational purposes as well. Staff are aware that there a likely errors in the ICD-10 codes on the Prioritized List and will be working diligently to correct these. Any errors found should be forwarded to staff.

  The 2016 CPT codes are now available and being reviewed by staff. Hodges asked that the straightforward codes be sent to committee members for review and comment prior to the meeting in November. Smits replied that she will send out a spreadsheet with the 2016 CPT codes with suggested placement once she has been able to do an initial review. This list may include all codes or just straightforward codes, depending on the complexity of the review.

The Oral Health Advisory Panel (OHAP) and Behavioral Health Advisory Panel (BHAP) met and their recommendations are included in the VbBS meeting materials. The obesity taskforce is being constituted with a first meeting planned for the winter.

Gary Allen, DMD, has been senate approved for membership on the HERC. The HERC will be asked to appoint him to the VbBS at their meeting later today, to replace James Tyack, DMD, as the dental expert on the subcommittee.

The errata document was reviewed and there was no discussion.

- **Topic: Straightforward/Consent Agenda**

  Discussion: There was no discussion about the consent agenda items.

  Recommended Actions:
  1. Add 43771 (Laparoscopy, surgical, gastric restrictive procedure; revision of adjustable gastric restrictive device component only) to line 428 COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT
  2. Add 93740 to the Services Recommended for Non-Coverage (SRNC) Table
  3. Advise Health Services Division (HSD) to remove 93740 (Temperature gradient studies) from the Diagnostic Procedures File
  4. Advise HSD to move 76831 (Saline infusion sonohysterography (SIS), including color flow Doppler, when performed) from the Ancillary File to the Diagnostic Workup File
  5. Add 58321-58323 (Artificial insemination) to the SRNC
  6. Advise HSD to remove 58321-58323 from the Ancillary File

MOTION: To approve the recommendations stated in the consent agenda. CARRIES 7-0.

- **Topic: 2016 CDT codes and OHAP report**

  Discussion: Smits reviewed a spreadsheet with the OHAP recommendations for placement of the 2016 CDT codes, and a document reviewing placement recommendations for CDT codes appearing on both the Prioritized List and one of the HSD code files. There was no discussion about these documents.

  Silver diamine fluoride (SDF) was discussed in detail. Bruce Austen, DMD, the dental director for OHA, testified that silver diamine fluoride does turn caries black, but arrests the decay process. Dentists can do a second step to clear out the decay and add a more cosmetically acceptable filling. However, the SDF allows the dentist to avoid anesthetics

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and drilling in young children and in the elderly. This makes caries arrest more readily available and more acceptable to the patient and less traumatic. He is in favor of SDF coverage and feels that medicaments are a new paradigm in the treatment of decay.

Smits noted that the medicaments must currently be applied by dental trained personnel. It is very easy to apply and may be done by non-trained personnel in the future, for example in the school.

Gibson asked for relative cost information vs. standard restoration. Austen responded that SDF is very cost effective, with a 100 dose bottle costing about $125. There is also no dental office time, anesthetic costs, etc.

Karen Nolan, who is an OHAP member, testified on behalf of her employer, ODS. ODS is not in favor of covering SDF. ODS dentists are concerned as it discolors teeth. Patients will need fillings eventually, so it will not save costs and will add cost for the exams and application twice a year on top of the usual filling costs. ODS feels that this treatment is experimental.

It was noted that Gary Allen, who is a member of OHAP and will be joining the HERC, has a conflict of interest regarding SDF as his company markets this product. Coffman noted that Dr. Allen had planned to recuse himself from any vote on this topic.

Recommended Actions:

1. Placement of 2016 CDT codes as shown in Appendix A
2. For CDT codes appearing on the Prioritized List and one of the HSD coding files, remove those codes from all other coding files and keep on their current line location on the Prioritized List
3. Add a new guideline for silver diamine fluoride as shown in Appendix B
4. Delete GN 91

MOTION: To recommend the code and guideline note changes as presented. CARRIES 7-0.

- **Topic: 2016 CPT codes**

Discussion: This section was informational only. HERC staff will bring back these codes for official approval with the other 2016 CPT codes at the November 2015 VbBS meeting.

The group discussed fetal MRI. There was discussion about the proposed guideline note. The group felt that there should be a requirement for two physicians, one a fetal or pediatric radiologist, to agree on the medical necessity of the MRI. Hodges requested that a clause be added requiring >17 weeks of estimated fetal age. There were

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questions about any specific requirements for the MRI machine, the training of the MRI tech or the reading radiologist. HERC staff were directed to reach out to radiologist and maternal-fetal medicine specialists to determine the best guideline wording.

High dose radionucleotide skin surface brachytherapy was briefly discussed. The subcommittee agreed with the staff recommendation to place on the Services Recommended for Non-Coverage Table.

Intravasular non-coronary ultrasound was discussed. There was a question about whether a guideline should be developed to limit the vessels in which this could be used. The thought was that this would be difficult to determine and the code should be suggested for the Diagnostic Procedures File.

Reflectance confocal microscopy for skin lesions was briefly discussed. The subcommittee agreed that this procedure was experimental and should be placed on the Services Recommended for Non-Coverage Table.

Intrastromal corneal ring segments was reviewed without substantive discussion. The subcommittee agreed that this procedure should be added to the line containing keratoconus with the proposed guideline.

Recommended Actions:
HERC staff will further research the 2016 CPT codes and bring recommendations for the entire set to the next VBBS meeting.

- **Topic: Temporary prostatic stents**

Discussion: Smits reviewed the summary document. There was minimal discussion.

Recommended Action:
Delete temporary prostatic stents (CPT 53855) from lines 332 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION and 334 CANCER OF PROSTATE GLAND and add to the Services Recommended for Non-Coverage Table as investigational.

MOTION: To recommend the code changes as presented. CARRIES 7-0.

- **Topic: Vertebral fracture assessment**

Discussion: Smits reviewed the summary document. There was minimal discussion.

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Recommended Actions:

a. Place CPT 77086 (Vertebral fracture assessment via dual-energy X-ray absorptiometry (DXA)) on the Services Recommended for Non-coverage Table as experimental
2. Advise HSD to remove CPT 77086 from the Diagnostic Procedures File

MOTION: To recommend the code changes as presented. CARRIES 7-0.

- **Topic: Optic neuritis**

Discussion: Smits reviewed the summary document. Pollack requested that the ophthalmology codes proposed for the Diagnostic Procedures File be reviewed in a year to see if they are being abused.

Recommended Actions:

1. Do not change the current prioritization of optic neuritis on line 654 INTRACRANIAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
2. Advise HSD to add ophthalmology evaluation CPT codes to the Diagnostic Procedures File; also keep these codes on current lines on the Prioritized List as done with other evaluation and management codes
   a. 92002, 92004, 92012, 92014 (Ophthalmological services: medical examination and evaluation, new and established patients)
   b. 92081-92083 (Visual field examination)
   c. 92100 (Serial tonometry for intraocular pressure measurement)
   d. 92140 (Provocative tests for glaucoma)
   e. 92133-92134 (Scanning computerized ophthalmic diagnostic imaging, posterior segment, with interpretation and report, unilateral or bilateral; optic nerve or retina)
3. Adopt a new diagnostic guideline for ophthalmology visits as shown in Appendix B

MOTION: To recommend the code and guideline note changes as presented. CARRIES 7-0.

- **Topic: Trochanteric bursitis**

Discussion: Smits reviewed the summary document. There was minimal discussion.

Recommended Actions:

1. Remove CPT 27062 (Excision; trochanteric bursa or calcification) from line 431 ACUTE PERIPHERAL MOTOR AND DIGITAL NERVE INJURY
2. Add CPT 20611 (Arthrocentesis, aspiration and/or injection, major joint or bursa (eg, shoulder, hip, knee, subacromial bursa); with ultrasound guidance) to line 381

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DISRUPTIONS OF THE LIGAMENTS AND TENDONS OF THE ARMS AND LEGS, EXCLUDING THE KNEE, RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT

3. Add trochanteric bursitis (ICD-10 M70.6x, M70.7x) to line 508 PERIPHERAL ENTHESOPATHIES Treatment: SURGICAL THERAPY
4. Adopt the new guideline regarding trochanteric bursitis as shown in Appendix B

MOTION: To recommend the code and guideline note changes as presented. CARRIES 7-0.

- **Topic: Nose repair**

Discussion: Smits reviewed the summary document. There was minimal discussion.

Recommended Actions:

1. Guideline note 80 was modified as shown in Appendix C
2. Guideline note 81 was deleted as shown in Appendix D
3. ICD-10 Q30.1 (Agenesis and underdevelopment of nose), Q30.2 (Fissured, notched and cleft nose), and Q30.8 (Other congenital malformations of nose) were deleted from line 261 DEFORMITIES OF HEAD
4. ICD-10 Q30.2 was added to line 305 CLEFT PALATE AND/OR CLEFT LIP
5. ICD-10 Q30.8 was added to lines 509 NASAL POLYPS, OTHER DISORDERS OF NASAL CAVITY AND SINUSES and 578 DEVIATED NASAL SEPTUM, ACQUIRED DEFORMITY OF NOSE, OTHER DISEASES OF UPPER RESPIRATORY TRACT
6. CPT 30430 (Rhinoplasty, secondary; minor revision (small amount of nasal tip work)) was removed from all lines and placed on the Services Recommended for Non-Coverage List
7. CPT 30460 (Rhinoplasty for nasal deformity secondary to congenital cleft lip and/or palate, including columellar lengthening; tip only) and 30462 (Rhinoplasty for nasal deformity secondary to congenital cleft lip and/or palate, including columellar lengthening; tip, septum, osteotomies) were removed from lines 469 CHRONIC SINUSITIS and 509 NASAL POLYPS, OTHER DISORDERS OF NASAL CAVITY AND SINUSES

MOTION: To recommend the code and guideline note changes as presented. CARRIES 7-0.

- **Topic: Stem cell transplant for neuroblastoma**

Discussion: Smits reviewed the summary document. There was minimal discussion.
Note: The new guideline was amended to add the ICD-10 code.

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Recommended Actions:

1. Add stem cell transplantation (CPT 38204-38215, 38230-38241; HCPCS S2150) to line 264 CANCER OF ENDOCRINE SYSTEM, EXCLUDING THYROID; CARCINOID SYNDROME
2. Adopt a new guideline for line 264 as shown in Appendix B

MOTION: To recommend the code and guideline note changes as presented. CARRIES 7-0.

- **Topic: Integration of medical and mental health services for child abuse and neglect**

Discussion: Smits reviewed the summary document. There was minimal discussion.

Recommended Actions:

1. Delete diagnosis codes for child abuse and neglect from line 177 POSTTRAUMATIC STRESS DISORDER
   a. ICD-10 T74 series, T76 series (child neglect, child abuse, child sexual abuse)
2. Add mental health CPT codes to line 125 ABUSE AND NEGLECT
   a. CPT 90785 (interactive complexity)
   b. 90832-90840, 90846-90853 (psychotherapy, including family and group)
   c. 90882 (Environmental intervention for medical management purposes on a psychiatric patient's behalf with agencies, employers, or institutions)
   d. 90887 (Interpretation or explanation of results of psychiatric, other medical examinations and procedures)
   e. 96101 (psychological testing)
3. Delete GN25 as shown in Appendix D

MOTION: To recommend the code and guideline note changes as presented. CARRIES 7-0.

- **Topic: Acute substance intoxication and withdrawal**

Discussion: Smits reviewed the summary document. There was minimal discussion.

Recommended Action:

Rename line 69 SUBSTANCE-INDUCED DELIRIUM; SUBSTANCE INTOXICATION AND WITHDRAWAL

MOTION: To recommend the line title change as presented. CARRIES 7-0.

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- **Topic: Botulinum toxin for migraines and bladder conditions**

Discussion: Smits reviewed the summary document. Gibson voiced concerns about the poor quality of the underlying studies cited in the botulinum toxin for migraine review. He was concerned about covering this treatment at all given its questionable efficacy. Williams agreed that there was little evidence to support the use of botulinum toxin for migraines. Gibson recommended increasing the proposed reduction in migraine frequency required for continued therapy from the proposed 6 to 8, to better reflect the study findings. Gibson also expressed concern about the use of urinary frequency reductions as a requirement for continuation for botulinum toxin for bladder indications as this symptom may just be a variant of normal. However, it was pointed out that earlier in the guideline, use is restricted to specific bladder indications and Gibson agreed that frequency reduction was acceptable as an outcome for those conditions.

Karen Campbell from Allergan testified that botulinum toxin for bladder indications is reserved for patients failing oral medications, and the only alternative to botulinum injections is nerve stimulation or bladder surgery. She noted that one injection may provide symptom relief for 6 months or longer.

Ms. Campbell further testified that migraine patients must also fail oral therapy prior to consideration for botulinum toxin. The other possible treatments for these patients include nerve block or neurostimulation, reflecting that few other options exist for this group of patients. She testified that many patients continue to improve the more injections they have. The treatment for migraines involve 31 injections during the session, and patients are only likely to endure this amount of injections if the treatment is actually helpful. She did not agree with requiring a reduction in headache days as a requirement for continuing therapy. She testified that patients improve in other ways, such as improvement in the level of pain on headache days or in quality of life measures. They may have shorter headaches, less intense headaches, have better response to their acute headache pain medications, less disability and improved ability to work. Chronic migraine patients have hypersensitivity to stimuli, and botulinum toxin injections can gradually help this. Clinical trials and practice show that botulinum toxin injection may require 2-3 injection cycles to improve hypersensitivity and headaches. She felt that the HERC should base coverage on symptomatic and functional improvement for these patients. She was concerned that the proposed guideline would mean that patients with reductions of 4 or 5 headache days would not qualify for further treatment and yet would have quality of life improvements. She suggested that the committee review utilization in Oregon to see if this treatment is overused or high.

Jane Stevens from Allergan testified that most private insurance plans require a reduction of 7 headache days per month or 100 headache hours per month for continued coverage of botulinum toxin injections for migraines.

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The subcommittee debated whether to require a reduction of 6, 7 or 8 headache days per month for the migraine guideline. The reduction of 7 days was determined to be the best compromise.

The subcommittee debated about the number of incontinence incidents or episodes of urinary frequency required for the bladder conditions guideline. The group increased the reduction of frequency episodes to 8 and the incontinence episodes to 2 to better reflect the reductions seen with botulinum treatment in the clinical trials.

Recommended Actions:

1. Adopt a new guideline for line 414 as shown in Appendix B
2. Adopt a new guideline for line 331 as shown in Appendix B

MOTION: To recommend the guideline note changes as amended. CARRIES 7-0.

- **Topic: Coverage of perforations of the ear drum with hearing loss**

Discussion: Smits reviewed the summary document. There was minimal discussion.

Recommended Actions:

1. Add diagnosis codes for ear drum perforations/open wounds to lines 316 HEARING LOSS - AGE 5 OR UNDER and 450 HEARING LOSS - OVER AGE OF FIVE and keep on line 479 CHRONIC OTITIS MEDIA, OPEN WOUND OF EAR DRUM
   a. ICD-10 H72.xx (perforation of tympanic membrane) and S09.2xx (Traumatic rupture of unspecified ear drum)
2. Add treatment CPT codes for perforations/open wounds to lines 316 and 450
   a. 69610 (Tympanic membrane repair, with or without site preparation of perforation for closure, with or without patch)
   b. 69620 (Myringoplasty)
   c. 69631-69646 (Tympanoplasty with or without mastoidectomy)
3. Change the treatment description of lines 316 and 450 to MEDICAL THERAPY INCLUDING HEARING AIDS, LIMITED SURGICAL THERAPY
4. Adopt a new guideline note for lines 316, 450 and 479 as shown in Appendix B

MOTION: To recommend the code and guideline note changes as presented. CARRIES 7-0.

- **Topic: Acute peripheral nerve injury guideline**

Discussion: Smits reviewed the summary document. The subcommittee discussed the fact that the neurosurgeon who brought up the issue recommended extending the limit to 6 months and recommended that the guideline was modified only to extend the

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surgical period to 6 months, rather than the proposed 1 year. The exceptions process could be used for patients who are between 6 months and 1 year from injury.

Recommended Actions:

1. Modify GN133 as shown in Appendix C

MOTION: To recommend the guideline note changes as amended. CARRIES 7-0.

- **Topic: Tobacco cessation coverage and prevention**

  Discussion: This topic was tabled to the November, 2015 VBBS meeting

- **Topic: Tobacco use and elective surgery**

  Discussion: This topic was tabled to the November, 2015 VBBS meeting

- **Topic: Acupuncture guideline referral requirement**

  Discussion: Smits reviewed the summary document. There was discussion about whether acupuncturists can generate diagnosis codes, which are required to determine if a condition is covered by this guideline. If acupuncturists cannot make the diagnoses, then coverage of acupuncture must continue to be done by referral from a provider who can make diagnoses. Hodges argued that acupuncture should be covered like physical therapy; PT requires an ICD9/10 code from a provider and a referral/order. Ocker indicated that acupuncturists are capable of making certain diagnoses, but not complex diagnoses.

  It was also noted that the staff proposed changed all acupuncture indications to have 12 covered acupuncture sessions. This is in conflict with the new back conditions guideline, which allows up to 30 visits. Staff was advised to rework this portion of the guideline.

  Livingston recommended that retaining the referral requirement for pelvic pain during pregnancy was appropriate, as this symptom can be caused by many conditions, and should be evaluated by a maternity care provider first. Ocker raised no objections to this.

  Staff was directed to work with the HSD clinical services unit to determine what acupuncturists can diagnosis and code and how referrals should work for acupuncture.

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Recommended Actions:
HERC staff to research whether acupuncturists can make diagnoses and whether acupuncture services need a referral. This topic will be revisited at a future meeting.

- **Topic: Mental health guidelines for children**

Discussion: Smits briefly reviewed this topic which had been previously reviewed by BHAP. There was minimal discussion.

Recommended Actions:
1) Guideline note 20 ATTENTION DEFICIT/HYPERACTIVITY DISORDERS IN CHILDREN was amended as shown in appendix C
2) Guideline notes 28, 42 and 45 were deleted as shown in appendix D

- **Topic: Statement of Intent 3 - Behavioral Health Integration**

Discussion: Smits reviewed the summary document. There was minimal discussion.

Recommended Actions:
Delete SOI3 as shown in Appendix D

MOTION: To recommend the statement of intent be deleted as presented. CARRIES 7-0.

- **Topic: Breast augmentation and penile implant coverage for gender dysphoria**

Discussion: Smits reviewed the staff summary document. Gibson objected to adding coverage for breast augmentation, arguing that this service is not covered for other women with social functioning issues due to small breast size, and that this type of procedure is cosmetic. Hodges agreed that breast augmentation appears to be cosmetic and coverage for gender dysphoria is unfair to other women with breast size issues.

Dr. Megan Bird from Legacy testified that the goal of breast augmentation for patients with gender dysphoria is to reduce the dysphoria, suicide rates, and other negative outcomes. Breasts are an overwhelming cue for a person to be recognized by others as a women. She argued that lack of coverage will increase the risk of violence and is therefore a safety issue.

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Gibson raised concerns that the presence of breasts is a defining aspect of being a women. Williams argued that the coverage for adolescents to receive early hormone treatment should lessen the need for breast reconstructions.

Bird responded that access to hormones, specifically estrogen for breast development, is limited for many patients due to medical or other issues.

Olson noted breast reconstruction is covered for patients with breast cancer, and he was wondering whether gender dysphoria should be considered a biologic condition on par with breast cancer. He also noted that patients with gender dysphoria as a group have terrible outcomes with no treatment, which is not the case for other women with simple cosmetic breast concerns.

Bird argued that the improvement in outcomes reviewed in the studies by HERC included breast augmentation as a possible therapy. The reduction in suicide rates and other negative outcomes were based on access to a package of therapy which included breast augmentation.

Amy Penkin, LCSW, from OHSU testified that breast surgery actually treats the dysphoria, rather than just being for social passing. She argued that linking it to gender dysphoria sets it apart from the cosmetic use.

Gibson asked when breasts could be considered large enough to be adequate to address gender dysphoria. Bird responded that there are guidelines based on Tanner developmental stages. Stage 5 on the Tanner scale corresponds to adult female breasts. This is a structural assessment, rather than based on size.

Neola Young, from Basic Rights Oregon, testified that breast surgery is more important to many transgender women than other types of gender dysphoria surgery. It is an important service to offer to reduce self harm in this population.

The discussion on penile implants was short. Bird testified that the only entity covering this is the city of San Francisco and they require 2 physicians to agree that the procedure is necessary, a surgeon's note that the phallus is appropriate for the prostheses, and evidence that the patient has used and failed external support devices.

Recommended Actions:

1. Add coverage for breast augmentation for male to female patients
    a. CPT codes to add to line 317 GENDER DYSPHORIA (Jan. 1, 2016)
        i. 14000-14001 Adjacent tissue transfer or rearrangement, trunk
        ii. 15200-15201 Full thickness graft, free, including direct closure of donor site, trunk
        iii. 19316 Mastopexy
        iv. 19324-19325 Mammaplasty, augmentation

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v. 19340 Immediate insertion of breast prosthesis following mastopexy, mastectomy or in reconstruction
vi. 19342 Delayed insertion of breast prosthesis following mastopexy, mastectomy or in reconstruction

b. Modify GN127 as shown in Appendix C

2. Remove penile prostheses (CPT 54400, 54401, and 54405) from line 317

MOTION: To recommend the code and guideline note changes as presented (option B) for breast augmentation. CARRIES 4-3 (Opposed: Hodges, Williams, Gibson)

MOTION: To recommend the code changes as presented for penile prostheses. CARRIES 7-0.

- **Topic: Coverage Guidance—Planned Out-of-hospital births**

Discussion: Livingston presented the process overview, evidence summary and core issues addressed by public comment. Dr. Duncan Neilson was introduced as an appointed expert. He is the Clinical Vice President of surgical services of Legacy health system and an obstetrician/gynecologist. Dr. Neilson reviewed the history of this effort beginning with a legislative mandate that involved licensing direct entry midwives as of January 2015 and an Oregon Health Authority Licensed Direct Entry Midwifery Workgroup that recommended that HERC evaluate the evidence and update the appropriate risk criteria to try to ensure safe and effective planned out-of-hospital births.

The subcommittee discussed that these risk criteria are about coverage. A woman with risk criteria may choose to have a planned out-of-hospital birth, but this would not be covered by the Oregon Health Plan. There was an amendment made to the box language to clarify that the intent is about coverage.

Livingston proceeded to discuss the options, being explicit about which criteria needed to be ruled out and also allowing for ambiguity when certain criteria may remain unknown if there were not clinical suspicion that would indicate a workup was appropriate. The example of ultrasound was discussed and the subcommittee agreed that it would be necessary to rule out certain risk criteria. Livingston highlighted some of the risk criteria that had received more public comment as well as some suggestions for clarifying language.

There was a discussion as to whether lethal congenital anomalies with planned nonrescucitation would be appropriate for coverage in an out-of-hospital birth setting. Kim Wentz stated that there are times when the prenatal diagnosis is wrong or the parents change their mind when the baby is born. Neilson stated that there are some lethal congenital anomalies that are more black and white and others that are gray.

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Also, in some cases it may be more explicit that nonresuscitation is clearly appropriate and changes in diagnosis or management plans are highly unlikely. There was a discussion about preserving the autonomy of the mother if the fetus doesn't require treatment. Anencephaly was given as an example. After discussion the subcommittee decided to move the revised language including "nonresuscitation planned" to be a criterion requiring consultation.

There was a discussion of a series of criteria that may not be known if there was no clinical suspicion, but also needing to define what those clinical factors may be. In a discussion about intrauterine growth reduction (IUGR), initially there was a proposal to define concerning clinical signs such as fundal height <3 cm from estimated gestational age over two measurements; however, Neilson suggested that other factors besides fundal height may be important and the estimation of fetal weight is multimodal. The language was changed to state that serial fundal measurements are required, but not to define what exactly suspicion for IUGR would entail. It was concluded that both serial blood pressure measurements and serial fundal heights would be required in order to verify the absence or presence of this high risk criteria.

There was a discussion of the unknown syphilis, HIV, or Hepatitis B status and a proposal to add "positive" status to the coverage exclusion criteria. Members discussed whether appropriate care could be given to a positive mother in a home setting and they decided that given the potential risk to the fetus/infant and the potential for intervention, that these would be risk criteria that would exclude a woman from coverage. Syphilis was added based on a staff recommendation as a result of recent public health data showing an increase in syphilis in Oregon.

Pollack commented and others agreed that readability of the box language would be improved with categorizing of the risk conditions.

Public comment:

Jeannie Stagner, CNM, of Klamath Falls. She stated she has been a midwife for 33 years, starting as direct entry midwife and later serving as a consultant to the Arizona State Department of Health Services. She stated she does not have hospital privileges and has a licensed birth center. She expressed concerns that inadequate stakeholder representation was involved in the process, and that guidelines are attempting to change midwifery statutes. She stated that 100% of her patients would have been found ineligible according to consultation guidelines, specifically raising concerns about VBAC and women receiving outpatient mental health care. She also raised concerns about the availability of consultants, especially in rural communities.

Neilson reviewed the history of this process starting with the legislation, the development of the licensed direct entry midwifery workgroup, including involvement

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of stakeholders with midwifery representation, and how the HERC work results from those processes.

The subcommittee discussed revising the language around maternal mental illness. Pollack suggested requiring consultation in cases where there is suspicion for psychosis or self-harm. The subcommittee ran out of further discussion time.

There was a discussion about the word "compliance" and the feeling it invokes. It was clarified that this will serve as the basis for rules and compliance would be an appropriate choice of words.

Summary of changes agreed to prior to the end of the meeting:

- Clarify further that these high risk criteria relate to coverage
- Move life-threatening congenital anomalies (unless fatal anomalies with nonresuscitation planned) to consultation criteria
- Add that serial fundal height measurements and serial blood pressure measurements are required
- Add unknown, or positive, syphilis, HIV, or hepatitis B status to high risk coverage exclusion criteria
- Categorize risk conditions in box language to improve readability
- Discuss further modifying the language on maternal mental illness requiring outpatient psychiatric care

Discussion to continue at the November 12, 2015 VbBS/HERC meetings.

- **Topic: Coverage Guidance—Indications for proton beam therapy**

  Discussion: This topic was tabled until the November 2015 VbBS meeting

- **Public Comment:**

  No additional public comment was received.

- **Issues for next meeting:**

  -2016 CPT code placement
  -Tobacco cessation for procedures guideline
  -Tobacco cessation coverage and prevention guideline
  -Acupuncture guideline
  -Coverage guidances for proton beam therapy and planned out-of-hospital birth
  -Posterior tibialis tendonopathy

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-Adjustment disorder coding specification
-Feeding tube code placement review

- **Next meeting:**

  November 12, 2015 at Clackamas Community College, Wilsonville Training Center, Rooms 111-112, Wilsonville, Oregon, Rooms.

- **Adjournment:**

  The meeting adjourned at 1:15 PM.

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Appendix A
Recommended Placement of 2016 CDT Codes

CDT Code	Code Description	Suggested Placement
D0251	extra-oral posterior dental radiographic image	Diagnostic List
D0422	collection and preparation of genetic sample material for laboratory analysis and report	Services Recommended for Non-Coverage Table
D0423	genetic test for susceptibility to diseases – specimen analysis	Services Recommended for Non-Coverage Table
D1354	interim caries arresting medicament application	**348** DENTAL CONDITIONS (EG. CARIES, FRACTURED TOOTH) *Note: With guideline limiting to silver diamine fluoride only, used up to twice per year*
D4283	autogenous connective tissue graft procedure (including donor and recipient surgical sites) – each additional contiguous tooth, implant or edentulous tooth position in same graft site	**496** DENTAL CONDITIONS (EG. PERIODONTAL DISEASE)
D4285	non-autogenous connective tissue graft procedure (including recipient surgical site and donor material) – each additional contiguous tooth, implant or edentulous tooth position in same graft site	**496** DENTAL CONDITIONS (EG. PERIODONTAL DISEASE)
D5221	immediate maxillary partial denture – resin base (including any conventional clasps, rests and teeth)	**594** DENTAL CONDITIONS (EG. CARIES, FRACTURED TOOTH)
D5222	immediate mandibular partial denture – resin base (including any conventional clasps, rests and teeth)	**594** DENTAL CONDITIONS (EG. CARIES, FRACTURED TOOTH)
D5223	immediate maxillary partial denture – cast metal framework with resin denture bases (including any conventional clasps, rests and teeth)	**594** DENTAL CONDITIONS (EG. CARIES, FRACTURED TOOTH)
D5224	immediate mandibular partial denture – cast metal framework with resin denture bases (including any conventional clasps, rests and teeth)	**594** DENTAL CONDITIONS (EG. CARIES, FRACTURED TOOTH)
D7881	occlusal orthotic device adjustment	**552** TMJ DISORDER
D8681	removable orthodontic retainer adjustment	**47** CLEFT PALATE WITH AIRWAY OBSTRUCTION **305** CLEFT PALATE AND/OR CLEFT LIP **621** DENTAL CONDITIONS (EG. MALOCCLUSION)
D9223	deep sedation/general anesthesia – each 15 minute increment	Exempt List
D9243	intravenous moderate (conscious) sedation/analgesia – each 15 minute increment	Exempt List
D9932	cleaning and inspection of removable complete denture, maxillary	Services Recommended for Non-Coverage Table
D9933	cleaning and inspection of removable complete denture, mandibular	Services Recommended for Non-Coverage Table

Appendix A
Recommended Placement of 2016 CDT Codes

CDT Code	Code Description	Suggested Placement
D9934	cleaning and inspection of removable partial denture, maxillary	Services Recommended for Non-Coverage Table
D9935	cleaning and inspection of removable partial denture, mandibular	Services Recommended for Non-Coverage Table
D9943	occlusal guard adjustment	**650** DENTAL CONDITIONS WHERE TREATMENT RESULTS IN MARGINAL IMPROVEMENT

Appendix B

New Guideline Notes

DIAGNOSTIC GUIDELINE DXX, OPHTHALMOLOGY DIAGNOSTIC VISITS

Ophthalmology diagnostic visits (CPT 92002, 92004, 92012, 92014, 92081-92083, 92100, 92140, 92133, 92134) are covered for the evaluation of serious eye symptoms such as sudden vision loss or eye pain.

GUIDELINE XXX, CARIES ARRESTING MEDICAMENT APPLICATION

Line 348

D1354 is limited to silver diamine fluoride applications, with a maximum of two applications per year.

GUIDELINE NOTE XXX, TROCHANTERIC BURSITIS

Lines 381, 508

Trochanteric bursitis (enthesopathy of the hip, ICD-9 726.5/ ICD-10 M70.6x, M70.7x) is included on line 381 for pairing with physical therapy and steroid joint injections. Trochanteric bursitis is included on line 508 for pairing with surgical interventions (i.e. CPT 27062).

GUIDELINE NOTE XXX, STEM CELL TRANSPLANTATION FOR NEUROBLASTOMA

Line 264

Stem cell transplantation (CPT 38204-38215, 38230-38241) is only included on this line for treatment of high risk neuroblastoma (ICD-9 194.0/ICD-10 C74.xx).

GUIDELINE NOTE XXX, CHEMODENERVATION FOR CHRONIC MIGRAINE

Line 414

Chemodenervation for treatment of chronic migraine (CPT 64615) is included on this line for prophylactic treatment of adults who meet all of the following criteria:

1) have chronic migraine defined as headaches on at least 15 days per month of which at least 8 days are with migraine
2) has not responded to or have contraindications to at least three prior pharmacological prophylaxis therapies (beta-blocker, calcium channel blocker, anticonvulsant or tricyclic antidepressant)
3) treatment is administered in consultation with a neurologist or headache specialist.

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Appendix B

Treatment is limited to two treatments given 3 months apart. Additional treatment requires documented positive response to therapy. Positive response to therapy is defined as a reduction of at least 7 headache days per month compared to baseline headache frequency.

GUIDELINE NOTE XXX, CHEMODENERVATION OF THE BLADDER

Line 331

Chemodenervation of the bladder (CPT 52287) is included on this line only for treatment of idiopathic detrusor over-activity or neurogenic detrusor over-activity (ICD-9 596.5x/ICD-10-CM N32.81) in patients who have not responded to or been unable to tolerate at least two urinary incontinence antimuscarinic therapies (e.g. fesoterodine, oxybutynin, solifenacin, darifenacin, tolterodine, trospium). Treatment is limited to 90 days, with additional treatment only if the patient shows documented positive response. Positive response to therapy is defined as a reduction of urinary frequency of 8 episodes per day or urinary incontinence of 2 episodes per day compared to baseline frequency.

GUIDELINE NOTE XXX, EAR DRUM REPAIR

Lines 316,450,479

Repair of open wounds or perforations of the ear drum (ICD-9 384.2x, 389.02, 872.61, 872.71/ICD-10 H72.xx, S09.2xx) are only included on lines 316 and 450 when there is documented conductive hearing loss greater than or equal to 25dB persistent for more than three months. Otherwise, such repairs are included on line 479.

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Appendix C

Modified Guidelines

GUIDELINE NOTE 20, ATTENTION DEFICIT/HYPERACTIVITY DISORDERS IN CHILDREN ~~AGE FIVE AND UNDER~~

Line 126

~~When using~~ Use of ~~ICD-9-CM 314.9/~~ICD-10-CM F90.9, Attention deficit/hyperactivity disorder, unspecified type, in children age 5 and under~~, it~~ is appropriate only when the following apply:

- Child does not meet the full criteria for the full diagnosis because of their age.
- For children age 3 and under, when the child exhibits functional impairment due to hyperactivity that is clearly in excess of the normal activity range for age (confirmed by the evaluating clinician's observation, not only the parent/caregiver report), and when the child is very limited in his/her ability to have the sustained periods of calm, focused activity which would be expected for the child's age.

For children age 5 and under diagnosed with disruptive behavior disorders, including those at risk for ADHD, ~~F~~first line therapy is evidence-based, structured "parent-behavior training." ~~(i.e. Triple P (Positive Parenting of Preschoolers) Program, Incredible Years Parenting Program, Parent-Child Interaction Therapy and New Forest Parenting Program). The term "parent" refers to the child's primary care givers, regardless of biologic or adoptive relationship.~~ Second line therapy is pharmacotherapy.

For children age 6 and over who are diagnosed with ADHD, pharmacotherapy alone or pharmacotherapy with psychosocial/behavioral treatment are included on this line for first line therapy.

~~Use of ICD-9-CM 314.9/ICD-10-CM F90.9 for children age five and younger is limited to pairings with the following procedure codes:~~

- ~~Assessment and Screening: 90791, 90792, H0002, H0031, H0032, T1023~~
- ~~Family interventions and supports: 90832-90838, 90846, 90847, 90849, 90887, H0038, H0045, H2021, H2022, H2027, S5151, S9125, T1005~~
- ~~Group therapy: 90785, 90832-90838, 90853, 99201-99215, H2032~~
- ~~Medication management: 90832-90838, 99201-99215~~
- ~~Case Management: 90882, T1016~~
- ~~Provider/teacher care coordination: 99366, 99367, 99368~~
- ~~Interpreter Service: T1013~~

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/herc/Pages/blog-treatment-adhd.aspx

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Appendix C

GUIDELINE NOTE 80, REPAIR OF NOSE TIP

Line 305

Nose tip repair (CPT 30460) is included on this line only to be used in conjunction with codes 40700, 40701, 40702, or 40720~~or~~ . If not done in the context of a larger cleft palate/lip surgery, then nose tip repair is only included on this line if required for ~~subsequent~~ correction of physical functioning.

GUIDELINE NOTE 127, GENDER DYSPHORIA

Line 413

Hormone treatment with GnRH analogues for delaying the onset of puberty and/or continued pubertal development is included on this line for gender questioning children and adolescents. This therapy should be initiated at the first physical changes of puberty, confirmed by pubertal levels of estradiol or testosterone, but no earlier than Tanner stages 2-3. Prior to initiation of puberty suppression therapy, adolescents must fulfill eligibility and readiness criteria and must have a comprehensive mental health evaluation. Ongoing psychological care is strongly encouraged for continued puberty suppression therapy.

Cross-sex hormone therapy is included on this line for treatment of adolescents and adults with gender dysphoria who meet appropriate eligibility and readiness criteria. To qualify for cross-sex hormone therapy, the patient must:

1. have persistent, well-documented gender dysphoria
2. have the capacity to make a fully informed decision and to give consent for treatment
3. have any significant medical or mental health concerns reasonably well controlled
4. have a comprehensive mental health evaluation provided in accordance with Version 7 of the World Professional Association for Transgender Health (WPATH) Standards of Care (www.wpath.org).

Sex reassignment surgery is included for patients who are sufficiently physically fit and meet eligibility criteria. To qualify for surgery, the patient must:

1. have persistent, well documented gender dysphoria
2. have completed twelve months of continuous hormone therapy as appropriate to the member's gender goals unless hormones are not clinically indicated for the individual
3. have completed twelve months of living in a gender role that is congruent with their gender identity unless a medical and a mental health professional both determine that this requirement is not safe for the patient
4. have the capacity to make a fully informed decision and to give consent for treatment
5. have any significant medical or mental health concerns reasonably well controlled
6. for breast/chest surgeries, have one referral from a mental health professional provided in accordance with version 7 of the WPATH Standards of Care.

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7. for genital surgeries, have two referrals from mental health professionals provided in accordance with the version 7 WPATH Standards of Care.

Electrolysis (CPT 17380) is only included on this line for surgical site electrolysis as part of pre-surgical preparation for chest or genital surgical procedures also included on this line. It is not included on this line for facial or other cosmetic procedures or as pre-surgical preparation for a procedure not included on this line.

Mammoplasty (CPT 19316, 19324-19325, 19340, 19342, 19350, 19357-19380) is only included on this line when 12 continuous months of hormonal (estrogen) therapy has failed to result in breast tissue growth of Tanner Stage 5 on the puberty scale OR there is a medical contraindication to hormonal therapy.

GUIDELINE NOTE 133, ACUTE PERIPHERAL MOTOR AND DIGITAL NERVE INJURY

Lines 430,491,515,522,541

Repair of acute (< ~~8 weeks~~ 6 months) peripheral nerve injuries are included on Line 430. Non-surgical medical care of these injuries are included on Line 491. Chronic nerve injuries are included on Lines 515, 522 and 541.

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Appendix D

Deleted Guidelines

~~STATEMENT OF INTENT 3: INTEGRATED CARE~~

~~Recognizing that many individuals with mental health disorders receive care predominantly from mental health care providers, and recognizing that integrating mental and physical health services for such individuals promotes patient-centered care, the Health Evidence Review Commission endorses the incorporation of chronic disease health management support within mental health service systems. Although such supports are not part of the mental health benefit package, mental health organizations (MHOs) that elect to provide these services may report them using psychiatric rehabilitation codes which pair with mental health diagnoses. If MHOs choose to provide tobacco cessation supports, they should report these services using 99407 for individual counseling and S9453 for classes.~~

~~GUIDELINE NOTE 25, MENTAL HEALTH PROBLEMS IN CHILDREN AGE FIVE AND UNDER RELATED TO NEGLECT OR ABUSE~~

~~Line 177~~

~~ICD-10-CM T76.02xA and T76.02xD (Child neglect or abandonment, suspected), (ICD-10-CM T74.02xA and T74.02xD (Child neglect or abandonment, confirmed), T74.22xA and T74.22xD (Child sexual abuse, confirmed), T76.22xA and T76.22xD (Child sexual abuse, suspected), T76.12xD (Child physical abuse, suspected, subsequent encounter) or T74.12xA and T74.12xD (Child physical abuse, confirmed) and corresponding ICD-9-CM codes 995.52, 995.53, 995,54 and – 995.59, may be used in any children when there is evidence or suspicion of abuse or neglect. These codes are to be used when the focus of treatment is on the alleged child victim. This can include findings by child welfare of abuse or neglect; or statements of abuse or neglect by the child, the perpetrator, or a caregiver or collateral report. Although these diagnoses can be used preventively, i.e. for children who are not yet showing symptoms, presence of symptoms should be demonstrated for interventions beyond evaluation or a short-term child or family intervention.~~

~~The codes T74.02xA, T74.02xD, T74.02XA, T74.02XD, T74.22xA, T74.22xD, T76.22xA, T76.22xD, T76.12xA, T76.12xD, 74.12xA or T74.12xD and corresponding ICD-9-CM codes 995.52, 995.53, 995,54 and – 995.59 may be used in children age five and younger and, in these instances only, is limited to pairings with the following procedure codes:~~

- ~~Assessment and Screening: 90791, 90792, H0002, H0031, H0032, T1023~~
- ~~Family interventions and supports: 90832-90838, 90846, 90847, 90849, 90887, H0038, H0045, H2021, H2022, H2027, S5151, S9125, T1005~~
- ~~Individual counseling and therapy: 90785, 90832-90838, 99201-99215~~
- ~~Group therapy: 90832-90838, 90853, 90857, H2032~~
- ~~Case Management: 90882, T1016~~
- ~~Interpreter Service: T1013~~
- ~~Medication management is not indicated for these conditions in children age 5 and under.~~

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Appendix D

GUIDELINE NOTE 28, MOOD DISORDERS IN CHILDREN AGE EIGHTEEN AND UNDER

Line 207

The use of ICD-10-CM code F39 Unspecified Mood [Affective] Disorder/ICD-9-CM code 296.90, Unspecified Episodic Mood Disorder, is appropriate only for children 18 years old and under, who have functional impairment caused by significant difficulty with emotional regulation.

Use of ICD-10-CM F39/ICD-9-CM 296.90 is limited to pairings with the following procedure codes:

- Assessment and Screening: 90791, 90792, H0002, H0031, H0032, T1023
- Family interventions and supports: 90832-90838, 90846, 90847, 90849, 90887, H0038, H0045, H2021, H2022, H2027, S5151, S9125, T1005
- Individual Counseling and Therapy: 90785, 90832-90838, 99201-99215, H0004
- Group therapy: 90785, 90832-90838, 90853, 99201-99215, H2032
- Medication management: 99201-99215
- Case Management: 90882, T1016
- Interpreter Service: T1013

GUIDELINE NOTE 42, DISRUPTIVE BEHAVIOR DISORDERS IN CHILDREN AGE FIVE AND UNDER

Line 425

The use of ICD-10-CM code F91.9 Conduct disorder, unspecified/ICD-9-CM 312.9, Unspecified Disturbance of Conduct), is appropriate only for children five years old and under, who display sustained patterns of disruptive behavior beyond what is developmentally appropriate. Interventions should prioritize parent skills training in effective behavior management strategies or focus on other relational issues.

Use of F91.9/312.9 is limited to pairings with the following procedure codes:

- Assessment and Screening: 90791, 90792, H0002, H0031, H0032, T1023
- Family interventions and supports: 90832-90838, 90846, 90847, 90849, 90887, H0038, H0045, H2021, H2022, H2027, S5151, S9125, T1005
- Individual Counseling and Therapy:90785, 90832-90838, 99201-99215, H0004
- Group therapy: 90785, 90832-90838, 90853, 99201-99215, H2032
- Case Management: 90882, T1016
- Interpreter Service: T1013
- Medication management is not indicated for these conditions in children age 5 and under.

GUIDELINE NOTE 45, ADJUSTMENT REACTIONS IN CHILDREN AGE FIVE AND UNDER

Line 449

ICD-10-CM code F43.2x/ICD-9-CM 309.89 can be used for individuals of any age. However, when using it for children five years of age or younger, who have experienced abuse or neglect, the following must apply:

The child must demonstrate some symptoms of PTSD (such as disruption of his or her usual sleeping or eating patterns, or more increased irritability/lower frustration tolerance) but does not meet the full criteria for PTSD or any other disorder.

A) F43.2x/309.89 is limited to pairings with the following procedure codes:

- Assessment and Screening: 90791, 90792, H0002, H0031, H0032, T1023
- Group Therapy: 90785, 90832-90838, 90853, 99201-99215, H2032

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- Family Interventions and Supports: 90832-90838, 90846, 90847, 90849, 90887, H0038, H0045, H2021, H2022, H2027, S5151, S9125, T1005
- Case Management: 90882, T1016
- Interpreter Service: T1013
- Individual Counseling and Therapy: 90785, 90832-90838, 99201-99215
- Medication Management is not indicated for this condition in children five years of age or younger.

Note: Cessation of the traumatic exposure must be the first priority. Infants and toddlers may benefit from parental guidance regarding management of the child's symptoms, parental guidance around enhancing safety and stability in the child's environment, and therapeutic support for the parents.

ICD-10-CM codes Z62.82x (Parent-child conflict) and Z63.4 (Disappearance and death of family member), may only be used as secondary diagnoses to the primary diagnosis of F43.2x, and only for children five years of age or younger. Two ICD-9-CM codes, V61.20 (Counseling for Parent-Child Problem, Unspecified) and V62.82 (Bereavement, Uncomplicated), may only be used as secondary diagnoses to the primary diagnosis of 309.89 (Other specified adjustment reactions), and only for children five years of age or younger.

A) When using codes Z62.82x/V61.20, the following must apply:
   1) Service provision will have a clinically significant impact on the child.
   2) A rating of 40 or lower has been assessed on the PIR-GAS (Parent-Infant Relationship Global Assessment Scale).
   3) The same limitations in pairings to CPT and HCPCS codes as given for ICD-10-CM code F43.2x apply, with the only exception being that 90785 cannot be used.

B) When using ICD-10-CM Z63.4 (Disappearance and death of family member)/ICD-9-CM V62.82, the following must apply:
   1) The child exhibits a change in functioning subsequent to the loss of a primary caregiver;
   2) The child exhibits at least three of the following eight symptoms:
      a) Crying, calling and/or searching for the absent primary caregiver,
      b) Refusing attempts of others to provide comfort,
      c) Emotional withdrawal manifesting in lethargy, sad facial expression, and lack of interest in age-appropriate activities that do not meet mood disorder criteria,
      d) Disruptions in eating and sleeping that do not meet criteria for feeding and eating disorders of infancy or early childhood,
      e) Regression in or loss of previously achieved developmental milestones not attributable to other health or mental health conditions,
      f) Constricted range of affect not attributable to a mood disorder or PTSD,
      g) Detachment, seeming indifference toward, or selective "forgetting" of the lost caregiver and/or of reminders of the lost caregiver,
      h) Acute distress or extreme sensitivity in response to any reminder of the caregiver or to any change in a possession, activity, or place related to the lost caregiver;
   3) The symptoms in B(2) above are exhibited for most of the day and for more days than not, for at least 2 weeks.
   4) The same limitations in pairings to CPT and HCPCS codes as given for ICD-10-CM code F43.2x/ICD-9-CM code 309.89 apply.

Note: Intervention should include persons significantly involved in the child's care and include psychoeducation and developmentally specific guidance.

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Appendix D

~~**GUIDELINE NOTE 81, RECONSTRUCTION OF THE NOSE**~~

~~*Lines 261,648*~~

~~ICD-10-CM codes Q30.1, Q30.2 and Q30.8/ICD-9-CM code 748.1 are on this line only for reconstruction of absence of the nose and other severe nasal anomalies which significantly impair physical functioning.~~

~~**GUIDELINE NOTE 91, SILVER COMPOUNDS FOR DENTAL CARIES**~~

~~*Lines 57,347,348,473,599*~~

~~Silver compounds for dental caries prevention and treatment are not included on these or any lines on the Prioritized List for coverage consideration~~

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Section 2.0

Staff Report

November 2015 Prioritized List Errata

1. Moved ICD-10 H40.03x (anatomic narrow angle glaucoma) from line 148 to line 248 PRIMARY ANGLE-CLOSURE GLAUCOMA. Placed on line 143 GLAUCOMA, OTHER THAN PRIMARY ANGLE-CLOSURE during the 2013 new ICD-10 code review, but never approved by HERC. H40.03 needs to be on line 248 to pair with appropriate treatment CPT codes. The ICD-9 equivalent (365.02 Anatomical narrow angle borderline glaucoma) is currently on line 248.
2. Reference to Algorithm D1 was corrected in Guideline Note D1, and the algorithm was moved to appear along with the guideline rather than at the end of the diagnostic guideline notes section.
3. Erroneous ICD-10 codes have been removed from two lines:
    a. ICD-10-CM codes M20.039-M21.769 were removed from 391 DEFORMITY/CLOSED DISLOCATION OF MINOR JOINT AND RECURRENT JOINT DISLOCATIONS
    b. ICD-10-CM codes M22.2X1-M23.92 were removed from 362 DEFORMITY/CLOSED DISLOCATION OF MAJOR JOINT AND RECURRENT JOINT DISLOCATIONS
    c. These codes represent flat feet, bunions, and other hand and foot joint deformities. They remain on one or more uncovered lines.
4. ICD-10 Z63.4 (Disappearance and death of family member) and F43.8 (Other reactions to severe stress) were added to line 449 ADJUSTMENT DISORDERS to align with the existing coding specification. A diagnosis description in the coding specification was also corrected.
5. In guideline note 106, the link to the Bright Futures periodicity schedule was updated.
6. Line 563 Open Wound of Eardrum was included; the entire line had previously been omitted from the list.
7. N39.43 (post void dribbling), N39.44 (Nocturnal enuresis), and N39.45 (Continuous leakage) were removed from line 459 URINARY INCONTINENCE due to the lack of treatment for these conditions. It is recommended that the Health Systems Division place these codes on the Diagnostic Workup File.
8. C22.x (various liver cancer diagnoses) were added to line 320 CANCER OF LIVER. The ICD-9 equivalents were on that line. C22.x remains on line 565 CANCER OF LIVER AND INTRAHEPATIC BILE DUCTS Treatment: Liver Transplant

Section 3.0

Consent Agenda-

Straightforward Items

Straightforward Issues—November, 2015

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
33968, 33971, 33974 33977-33978 33980-33983	Removal of intra-aortic balloon assist device Removal of ventricular assist device; extracorporeal Removal or replacement of ventricular assist device pump(s); implantable intracorporeal	290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT	ICD-10 T82.897 (Other specified complication of cardiac prosthetic devices, implants and grafts) is on line 290. This diagnosis is used for complications related to ventricular assist devices. 33980-33983 are used for removal or replacement of VADS and currently appears on the three lines containing VAD placement CPT codes. The other CPT codes listed should also be on the complications line.	Add 33968, 33971, 33974, 33977, 33978, 33980-33983 to line 290
44372 44373	Small intestinal endoscopy, enteroscopy beyond second portion of duodenum, not including ileum; with placement of percutaneous jejunostomy tube with conversion of percutaneous gastrostomy tube to percutaneous jejunostomy tube	**75** NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL **105** CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION **383** ESOPHAGEAL STRICTURE; ACHALASIA	44372 is on lines 75, 105 and 383; 44373 is on lines 105 and 383. All other feeding tube placement CPT codes are Ancillary.	Remove 44372 from lines 75, 105 and 383 Remove 44373 from lines 105 and 383 Advise HSC to add 44372 and 44373 to the Ancillary List

Straightforward Issues—November, 2015

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
Z79.01	Long term (current) anticoagulation use	285 BUDD-CHIARI SYNDROME, AND OTHER VENOUS EMBOLISM AND THROMBOSIS	The icd-9 equivalent to Z79.01 (V58.61) was not on line 285; however this code is appropriate for this line. Z79.01 appears on multiple other lines.	Add Z79.01 to line 285
		422 DISORDERS OF SHOULDER, INCLUDING SPRAINS/STRAINS GRADE 3 THROUGH 6	GN 97 states that only sprains/strains grade 4-6 are included on this line.	Change the line title for line 422 DISORDERS OF SHOULDER, INCLUDING SPRAINS/STRAINS GRADE ~~3~~4 THROUGH 6
Z68.3x Z68.4x Z68.54	Body mass index (BMI) 30.0-39.9, adult Body mass index (BMI) 40.0+, adult Body mass index (BMI) pediatric, greater than or equal to 95th percentile for age	325 OBESITY (ADULT BMI ≥ 30, CHILDHOOD BMI ≥ 95 PERCENTILE) 589 OBESITY (ADULT BMI ≥ 30, CHILDHOOD BMI ≥ 95 PERCENTILE)	The obesity BMI diagnosis codes are all currently on the HSD Informational File. These codes can be used as a primary diagnosis code and should be included on the obesity lines.	Add Z68.3x and Z68.4x and Z68.54 to lines 325 and 589 Advise HSC to remove Z68.3x and Z68.4x and Z68.54 from the Informational File

Straightforward Back Lines Corrections

The following issues were found on review of the new back lines which will appear on the January 1, 2016 Prioritized List.

1) 97010 (Application of a modality to 1 or more areas; hot or cold packs) is not currently listed on any line on the 1/1/16 List. It previously was on one of the uncovered back lines
    a. HERC staff recommendation: place 97010 on line 663 MUSCULOSKELETAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENT
    b. Will review with other PT modalities and bring back to a future meeting
2) The new surgical back lines included all hospitalization CPT codes, but an incomplete set of codes was included in the meeting materials
    a. HERC staff recommendation: add 99291-99292 (Critical care, evaluation and management of the critically ill or critically injured patient) to lines
        i. 351 CONDITIONS OF THE BACK AND SPINE WITH URGENT SURGICAL INDICATIONS
        ii. 366 SCOLIOSIS
        iii. 532 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS
3) M54.11-M54.6 were listed on lines for the new back pain lines, but some of these codes were also listed on the Diagnostic Work up File. These codes were intended to be on the medical back pain line only.
    a. HERC staff recommendation: add M54.3x (Sciatica) and M54.4x (Lumbago) only on line 407 CONDITIONS OF THE BACK AND SPINE
4) M41.40, M41.50 are on line 366 SCOLIOSIS and also the HSD Undefined File. On review, the entire M41.xx series are listed on both line 366 SCOLIOSIS and line 407 CONDITIONS OF THE BACK AND SPINE. The intent was to have only on line 366.
    a. HERC staff recommendation:
        i. add M41.xx only to line 366 SCOLIOSIS
        ii. Add line 366 to the medical back line guideline
5) M40.10 and M54.10 are on the undefined file and line 407 and 532
    a. HERC staff recommendation: do not include M40.10 and M54.10 on the undefined file

Peripheral Vascular Disease Line Revisions

Issue: During the ICD-10 review, the vascular surgery group re-ordered the peripheral vascular disease lines, placing all diagnoses with rest pain, ulcer, gangrene or other limb threatening conditions into line 240 LIMB THREATENING VASCULAR DISEASE, INFECTIONS, AND VASCULAR COMPLICATIONS and all diagnoses without those complications into line 354 NON-LIMB THREATENING PERIPHERAL VASCULAR DISEASE. There have been multiple questions about these lines raised by the CCOs with ICD-10 implementation, and multiple errors found on HERC staff review. Mainly, the accepted change to separate the diagnoses based on complications was not carried out, and the amputation codes were never removed from the lower line as intended.

HERC staff recommendations:

1) Remove from line 240 LIMB THREATENING VASCULAR DISEASE, INFECTIONS, AND VASCULAR COMPLICATIONS and add to line 354 NON-LIMB THREATENING PERIPHERAL VASCULAR DISEASE.
    a. I70.20x Unspecified atherosclerosis of native arteries of extremities
    b. I70.29x Other atherosclerosis of native arteries of extremities
    c. I70.30x Unspecified atherosclerosis of unspecified type of bypass graft(s) of the extremities
    d. I70.39x Other atherosclerosis of unspecified type of bypass graft(s) of the extremities
    e. I70.40x Unspecified atherosclerosis of autologous vein bypass graft(s) of the extremities
    f. I70.49x Other atherosclerosis of autologous vein bypass graft(s) of the extremities
    g. I70.50x Unspecified atherosclerosis of nonautologous biological bypass graft(s) of the extremities
    h. I70.59x Other atherosclerosis of nonautologous biological bypass graft(s) of the extremities
    i. I70.60x Unspecified atherosclerosis of nonbiological bypass graft(s) of the extremities
    j. I70.69x Other atherosclerosis of nonbiological bypass graft(s) of the extremities
    k. I70.70x Unspecified atherosclerosis of other type of bypass graft(s) of the extremities
    l. I70.79x Other atherosclerosis of other type of bypass graft(s) of the extremities
    m. E11.51 Other specified diabetes mellitus with diabetic peripheral angiopathy without gangrene
2) Remove from line 354 and keep on line 240
    a. I70.21x Atherosclerosis of native arteries of extremities with intermittent claudication
    b. I70.31x Atherosclerosis of unspecified type of bypass graft(s) of the extremities with intermittent claudication
    c. I70.41x Atherosclerosis of autologous vein bypass graft(s) of the extremities with intermittent claudication

   d. I70.51x Atherosclerosis of nonautologous biological bypass graft(s) of the extremities with intermittent claudication
   e. I70.61x Atherosclerosis of nonbiological bypass graft(s) of the extremities with intermittent claudication
   f. I70.71x Atherosclerosis of other type of bypass graft(s) of the extremities with intermittent claudication
   g. I70.22x Atherosclerosis of native arteries of extremities with rest pain
   h. I70.32x Atherosclerosis of unspecified type of bypass graft(s) of the extremities with rest pain
   i. I70.42x Atherosclerosis of autologous vein bypass graft(s) of the extremities with rest pain
   j. I70.52x Atherosclerosis of nonautologous biological bypass graft(s) of the extremities with rest pain
   k. I70.62x Atherosclerosis of nonbiological bypass graft(s) of the extremities with rest pain
   l. I70.72x Atherosclerosis of other type of bypass graft(s) of the extremities with rest pain
   m. I70.26x Atherosclerosis of native arteries of extremities with gangrene
   n. I70.36x Atherosclerosis of unspecified type of bypass graft(s) of the extremities with gangrene
   o. I70.46x Atherosclerosis of autologous vein bypass graft(s) of the extremities with gangrene
   p. I70.56x Atherosclerosis of nonautologous biological bypass graft(s) of the extremities with gangrene
   q. I70.66x Atherosclerosis of nonbiological bypass graft(s) of the extremities with gangrene
   r. I70.76x Atherosclerosis of other type of bypass graft(s) of the extremities with gangrene
3) Add the following to line 240 and keep on current lines:
   a. E08.52 Diabetes mellitus due to underlying condition with diabetic peripheral angiopathy with gangrene
   b. E10.52 Type 1 diabetes mellitus with diabetic peripheral angiopathy with gangrene
   c. E11.52 Type 2 diabetes mellitus with diabetic peripheral angiopathy with gangrene
4) Add the following to line 354 and keep on current lines
   a. E08.51 Diabetes mellitus due to underlying condition with diabetic peripheral angiopathy without gangrene
   b. E09.51 Drug or chemical induced diabetes mellitus with diabetic peripheral angiopathy without gangrene
   c. E10.51 Type 1 diabetes mellitus with diabetic peripheral angiopathy without gangrene
5) Remove all amputation CPT codes from line 354

a. The ICD-10 recommendation summary contained conflicting recommendations for CPT code placement for line 354. The verbal summary stated that all interventions EXCEXPT amputations be included on this line, but the summary then went on to include a series of amputation CPT codes to add to this line. HERC staff believe the intent is to not have amputations on line 354 and all amputation CPT codes should be removed.
    i. 24900-24940
    ii. 25900-25931
    iii. 26910, 26951, 26952, 27025
    iv. 27290, 27295
    v. 27590-27598
    vi. 27880-28825

Section 4.0

New Codes

Code	Code description	Proposed Line	Comments
99415	Prolonged clinical staff service (the service beyond the typical service time) during an evaluation and management service in the office or outpatient setting, direct patient contact with physician supervision; first hour each additional 30 minutes	**E&M Lines**	
99416	each additional 30 minutes (List separately in addition to code for prolonged service)	**E&M Lines**	
10035	Placement of soft tissue localization device(s) (eg, clip, metallic pellet, wire/needle, radiative seeds), percutaneous, including imaging guidance; first lesion	**Diagnostic Procedures File**	Used for targeting lesions to assist in biopsies
10036	each additional lesion (List separately in addition to code for primary procedure)	**Diagnostic Procedures File**	See 10035
33477	Transcatheter pulmonary valve implantation, percutaneous approach, including pre-stenting of the valve delivery site, when performed	**73** ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION **86** MYOCARDITIS, PERICARDITIS, AND ENDOCARDITIS **115** CONGENITAL HEART BLOCK; OTHER OBSTRUCTIVE ANOMALIES OF HEART **190** RHEUMATIC MULTIPLE VALVULAR DISEASE **193** CHRONIC ISCHEMIC HEART DISEASE **262** DISEASES OF MITRAL, TRICUSPID, AND PULMONARY VALVES **290** COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT	The open equivalent, 33475 (replacement of pulmonary valve) is on lines 73,86,115,190,193,262,290
37252	Intravascular ultrasound (noncoronary vessel) during diagnostic evaluation and/or therapeutic intervention, including radiological supervision and interpretation; initial noncoronary vessel	**Diagnostic Procedures File**	Discussed at October 2015 VBBS meeting

Code	Code description	Proposed Line	Comments
37253	each additional noncoronary vessel (List separately in addition to code for primary procedure)	**Diagnostic Procedures File**	Discussed at October 2015 VBBS meeting
39401	Mediastinoscopy; includes biopsy(ies) of mediastinal mass (eg, lymphoma), when performed	**Diagnostic Procedures File**	Replaces 39400 (Mediastinoscopy, includes biopsy(ies), when performed) which was diagnostic
39402	with lymph node biopsy(ies) (eg, lung cancer staging)	**Diagnostic Procedures File**	See 39401
43210	Esophagogastroduodenoscopy with esophagogastric fundoplasty, partial or complete, includes duodenoscopy when performed	**60** ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE **385** ESOPHAGITIS; ESOPHAGEAL AND INTRAESOPHAGEAL HERNIAS	Similar code 43280 (Laparoscopy, sugical, esophagogastric fundoplasty) is on lines 60,385
47531	Injection procedure for cholangiography, percutaneous, complete diagnostic procedure including imaging guidance (eg, ultrasound and/or fluoroscope) and all associated radiological supervision and interpretation; existing access	**Diagnostic Procedures File**	Replaces 47500 (Injection procedure for percutaneous transhepatic cholangiography) which was Diagnostic. Combines procedure with radiological supervision (74320)
47532	new access(eg, percutaneous transhepatic cholangiogram)	**Diagnostic Procedures File**	Similar to deleted code 47500 which was diagnostic.
47533	Placement of biliary drainage catheter, percutaneous, including diagnostic cholangiography when performed, including diagnostic cholangiography when performed, imaging guidance (eg, ultrasound and/or fluoroscopy), and all associated radiological supervision and interpretation; external	**59** COMPLICATED STONES OF THE GALLBLADDER AND BILE DUCTS; CHOLECYSTITIS **84** INJURY TO INTERNAL ORGANS **105** CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION **298** ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER **320** CANCER OF LIVER **439** CANCER OF GALLBLADDER AND OTHER BILIARY	Replaces 47510 (Introduction of percutaneous transhepatic catheter for biliary drainage) which was on lines 59, 84, 105, 298, 439. Combines intervention with previously separate radiology supervision code (75980) Line 320 is also appropriate for this procedure

Code	Code description	Proposed Line	Comments
47534	internal - external	**59** COMPLICATED STONES OF THE GALLBLADDER AND BILE DUCTS; CHOLECYSTITIS **105** CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION **298** ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER **320** CANCER OF LIVER **439** CANCER OF GALLBLADDER AND OTHER BILIARY	Replaces 47511 (Introduction of percutaneous transhepatic stent for internal and external biliary) which was on lines 59, 105, 298, 439. Combines intervention with previously separate radiology supervision code (75982) Line 320 is also appropriate for this procedure
47535	Conversion of external biliary drainage catheter to internal-external biliary drainage catheter, percutaneous, including diagnostic cholangiography when performed, imaging guidance (eg, fluoroscopy), and all associated radiological supervision and interpretation	**59** COMPLICATED STONES OF THE GALLBLADDER AND BILE DUCTS; CHOLECYSTITIS **105** CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION **298** ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER **439** CANCER OF GALLBLADDER AND OTHER BILIARY	Similar to 47530 (Revision and/or reinsertion of transepatic tube) which is on lines 59, 105, 298, 439.

Code	Code description	Proposed Line	Comments
47536	Exchange of biliary drainage catheter (eg, external, internal-external, or conversion of internal-external to external only), percutaneous, including diagnostic cholangiography when performed, imaging guidance (eg, fluoroscopy), and all associated radiological supervision and interpretation	**59** COMPLICATED STONES OF THE GALLBLADDER AND BILE DUCTS; CHOLECYSTITIS **105** CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION **298** ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER **320** CANCER OF LIVER **428** COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT **439** CANCER OF GALLBLADDER AND OTHER BILIARY	Replaces 47525 (Change of percutaneous biliary drainage catheter) which was on lines 59,105,298,428,439. Combines procedure with radiologic supervision (75984) Line 320 is also appropriate for this procedure
47537	Removal of biliary drainage catheter, percutaneous, requiring fluoroscopic guidance (eg, with concurrent indwelling biliary stents), including diagnostic cholangiography when performed, imaging guidance (eg, fluoroscopy), and all associated radiological supervision and interpretation	**59** COMPLICATED STONES OF THE GALLBLADDER AND BILE DUCTS; CHOLECYSTITIS **84** INJURY TO INTERNAL ORGANS **105** CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION **298** ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER **320** CANCER OF LIVER **428** COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT **439** CANCER OF GALLBLADDER AND OTHER BILIARY	No previous removal CPT code. Line recommendations are all lines containing placmenet of biliary drainage catheters as well as the complications line Line 320 is also appropriate for this procedure

Code	Code description	Proposed Line	Comments
47538	Placement of stent(s) into bile duct, percutaneous, including diagnostic cholangiography, imaging guidance (eg, fluoroscopy and/or ultrasound), balloon dilation, catheter exchange(s) and catheter removal(s) when performed, and all associated radiological supervision and interpretation, each stent; existing access	**59** COMPLICATED STONES OF THE GALLBLADDER AND BILE DUCTS; CHOLECYSTITIS **105** CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION **298** ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER **320** CANCER OF LIVER **439** CANCER OF GALLBLADDER AND OTHER BILIARY	Similar code 47801 (Placement of choledochal stent) is on lines 59,105,298. Added line 439 as this line is appropriate. Line 320 is also appropriate for this procedure
47539	new access, without placement of separate biliary drainage catheter	**59** COMPLICATED STONES OF THE GALLBLADDER AND BILE DUCTS; CHOLECYSTITIS **105** CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION **298** ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER **320** CANCER OF LIVER **439** CANCER OF GALLBLADDER AND OTHER BILIARY	See 47538

Code	Code description	Proposed Line	Comments
47540	new access, with placement of separate biliary drainage catheter (eg, external or internal - external)	**59** COMPLICATED STONES OF THE GALLBLADDER AND BILE DUCTS; CHOLECYSTITIS **105** CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION **298** ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER **320** CANCER OF LIVER **439** CANCER OF GALLBLADDER AND OTHER BILIARY	See 47538
47541	Placement of access through the biliary tree and into small bowel to assist with an endoscopic biliary procedure (eg, rendezvous procedure), percutaneous, including diagnostic cholangiography when performed, imaging guidance (eg, ultrasound and/or fluoroscopy), and all associated radiological supervision and interpretation, new access	**Diagnostic Procedures File**	Biliary endoscopy is Diagnostic (CPT 47550-47553) or on lines 59,105,298 if stenting is preformed (CPT 47554-47556)

Code	Code description	Proposed Line	Comments
47542	Balloon dilation of biliary duct(s) or of ampulla (sphincteroplasty), percutaneous, including imaging guidance (eg, Fluoroscopy), and all associated radiological supervision and interpretation, each duct (List separately in addition to code for primary procedure)	**59** COMPLICATED STONES OF THE GALLBLADDER AND BILE DUCTS; CHOLECYSTITIS **105** CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION **194** NEOPLASMS OF ISLETS OF LANGERHANS **199** ACUTE PANCREATITIS **255** CHRONIC PANCREATITIS **290** COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT **298** ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER **320** CANCER OF LIVER **321** CANCER OF PANCREAS **439** CANCER OF GALLBLADDER AND OTHER BILIARY **645** GALLSTONES WITHOUT CHOLECYSTITIS	Similar code 43262 (Endoscopic retrograde cholangiopancreatography (ERCP); with sphincterotomy/papillotomy) is on lines 59,194,199,255,290,298,321,439, 645 Similar code 47555 (Biliary endoscopy with dilateiron of biliary duct strictures) is on lines 59,105,298 Similar code 43277 (Endoscopic retrograde cholangiopancreatography (ERCP); with trans-endoscopic balloon dilation of biliary/pancreatic duct(s) or of ampulla (sphincteroplasty), including sphincterotomy) is on lines 59,194,199,255,290,298,320,321, 439, 645
47543	Endoluminal biopsy(ies) of biliary tree, percutaneous, and method(s) (eg, brush, forceps, and/or needle), including imaging guidance (eg, fluoroscopy), and all associated radiological supervision and interpretation, single or multiple (List separately in addition to code for primary procedure)	**Diagnostic Procedures File**	Endoscopic version of this procedure (47553) is diagnostic

Code	Code description	Proposed Line	Comments
47544	Removal of calculi/debris from biliary duct(s) and/or gallbladder, percutaneous, including destruction of calculi by method (eg, mechanical , electrohydraulic lithotripsy) when performed, imaging guidance (eg, fluoroscopy), and all associated radiological supervision and interpretation (List separately in addition to code for primary procedure)	**59** COMPLICATED STONES OF THE GALLBLADDER AND BILE DUCTS; CHOLECYSTITIS **105** CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION **298** ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER	Similar code 47554 (Biliary endoscopy, percutaneous via T-tube or other tract; with removal of calculus/calculi) is on lines 59,105,298
50430	Injection procedure for antegrade nephrostogram and/or ureterogram, complete diagnostic procedure including imaging guidance (eg, ultrasound and fluoroscopy) and all associated radiological supervision and interpretation; new access	**Diagnostic Procedures File**	Replaces 50394 (Injection procedure for pyelography (as nephrostogram, pyelostogram, antegrade pyeloureterograms) through nephrostomy or pyelostomy tube, or indwelling ureteral catheter) which was Diagnostic. Bundles in radiologic supervision
50431	existing access	**Diagnostic Procedures File**	See 50430
50432	Placement of nephrostomy catheter, percutaneous, including diagnostic nephrostogram and/or ureterogram when performed, imaging guidance (eg, ultrasound and/or fluoroscopy) and all associated radiological supervision and interpretation	**184** URETERAL STRICTURE OR OBSTRUCTION; HYDRONEPHROSIS; HYDROURETER **235** URINARY FISTULA **357** URINARY SYSTEM CALCULUS	Replaces 50393 (Introduction of ureteral catheter or stent into ureter through renal pelvis for drainage and/or injection, percutaneous) which was on lines 184,357. Bundles in radiologic supervision. Line 235 also contains other nephrostomy CPT codes

Code	Code description	Proposed Line	Comments
50433	Placement of nephroureteral catheter, percutaneous, including diagnostic nephrostogram and/or ureterogram when performed, imaging guidance (eg, ultrasound and/or fluoroscopy) and all associated radiological supervision and interpretation, new access	**184** URETERAL STRICTURE OR OBSTRUCTION; HYDRONEPHROSIS; HYDROURETER **235** URINARY FISTULA **357** URINARY SYSTEM CALCULUS	See 50432
50434	Convert nephrostomy catheter to nephroureteral catheter, percutaneous, including diagnostic nephrostogram and/or ureterogram when performed, imaging guidance (eg, ultrasound and/or fluoroscopy) and all associated radiological supervision and interpretation, via pre-existing nephrostomy tract	**184** URETERAL STRICTURE OR OBSTRUCTION; HYDRONEPHROSIS; HYDROURETER **235** URINARY FISTULA **357** URINARY SYSTEM CALCULUS	See 50432
50435	Exchange nephrostomy catheter, percutaneous, including diagnostic nephrostogram and/or ureterogram when performed, imaging guidance (eg, ultrasound and/or fluoroscopy) and all associated radiological supervision and interpretation	**184** URETERAL STRICTURE OR OBSTRUCTION; HYDRONEPHROSIS; HYDROURETER **235** URINARY FISTULA **290** COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT **357** URINARY SYSTEM CALCULUS	Replaces 50398 (Change of nephrostomy or pyelostomy tube) which was on lines 75,184,235,290. Of these, 184, 235, and 290 are appropriate. Other nephrostomy CPT codes are on line 357
50606	Endoluminal biopsy of ureter and/or renal pelvis, non-endoscopic, including imaging guidance (eg, ultrasound and/or fluoroscopy) and all associated radiological supervision and interpretation (List separately in addition to code for primary procedure)	**Diagnostic Procedures File**	

Code	Code description	Proposed Line	Comments
50693	Placement of ureteral stent, percutaneous, including diagnostic nephrostogram and/or ureterogram when performed, imaging guidance (eg, ultrasound and/or fluoroscopy), and all associated radiological supervision and interpretation ; pre-existing nephrostomy tract	**51** DEEP ABSCESSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS **53** CONGENITAL HYDRONEPHROSIS **84** INJURY TO INTERNAL ORGANS **184** URETERAL STRICTURE OR OBSTRUCTION; HYDRONEPHROSIS; HYDROURETER **275** CANCER OF BLADDER AND URETER **357** URINARY SYSTEM CALCULUS	Similar codes 50605 (Ureterotomy for insertion of indwelling stent, all types) is on lines 53,184,275,357. Similar code 52332 (Cystourethroscopy, with insertion of indwelling ureteral stent) is on lines 51,84,184,275,357
50694	new access, without separate nephrostomy catheter	**51** DEEP ABSCESSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS **53** CONGENITAL HYDRONEPHROSIS **84** INJURY TO INTERNAL ORGANS **184** URETERAL STRICTURE OR OBSTRUCTION; HYDRONEPHROSIS; HYDROURETER **275** CANCER OF BLADDER AND URETER **357** URINARY SYSTEM CALCULUS	See 50693
50695	new access with separate nephrostomy catheter	**51** DEEP ABSCESSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS **53** CONGENITAL HYDRONEPHROSIS **84** INJURY TO INTERNAL ORGANS **184** URETERAL STRICTURE OR OBSTRUCTION; HYDRONEPHROSIS; HYDROURETER **275** CANCER OF BLADDER AND URETER **357** URINARY SYSTEM CALCULUS	See 50693
50706	Balloon dilation, ureteral stricture, including imaging guidance (eg, ultrasound and/or fluoroscopy) and all associated radiological supervision and interpretation (List separately in addition to code for primary procedure)	**184** URETERAL STRICTURE OR OBSTRUCTION; HYDRONEPHROSIS; HYDROURETER **332** FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION	Ureteral stricture diagnosis codes appear on lines 184 and 332

Code	Code description	Proposed Line	Comments
54437	Repair of traumatic corporeal tear(s)	**212** DEEP OPEN WOUND, WITH OR WITHOUT TENDON OR NERVE INVOLVEMENT **332** FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION	Line 332 contains the CPT codes for repair of the urethra. Line 212 contains "deep open wound of penis"
54438	Replantation, penis, complete amputation including urethral repair	**212** DEEP OPEN WOUND, WITH OR WITHOUT TENDON OR NERVE INVOLVEMENT **332** FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION	ICD-10 S38.221 (complete amputation fo penis) is on line 212 DEEP OPEN WOUND, WITH OR WITHOUT TENDON OR NERVE INVOLVEMENT and 337 CONDITIONS REQUIRING HYPERBARIC OXYGEN THERAPY Line 332 contains the CPT codes for repair of the urethra
65785	Implantation of intrastromal corneal ring segments	**Services Recommended for Non-Coverage Table**	Discussed at October 2015 VBBS meeting
69209	Removal impacted cerumen using irrigation/lavage, unilateral	**316** HEARING LOSS - AGE 5 OR UNDER 395 ACUTE OTITIS MEDIA **432** NON-MALIGNANT OTITIS EXTERNA **450** HEARING LOSS - OVER AGE OF FIVE **479** CHRONIC OTITIS MEDIA; OPEN WOUND OF EAR DRUM **503** CERUMEN IMPACTION	69210 (Removal impacted cerumen requiring instrumentation, unilateral) is on 316,395,432,450,479,503
72081	Radiologic examination, spine, entire thoracic and lumbar, including skull, cervical and sacral spine if performed (eg, scoliosis evaluation); one view	**Diagnostic Procedures File**	Replaces deleted codes 72069-72090 (Radiologic examination, spine, thoracolumbar, standing (scoliosis), various views) which were diagnostic
72082	2 or 3 views	**Diagnostic Procedures File**	See 72081
72083	4 or 5 views	**Diagnostic Procedures File**	See 72081
72084	minimum of 6 views	**Diagnostic Procedures File**	See 72081

Code	Code description	Proposed Line	Comments
73501	Radiologic examination, hip, unilateral, with pelvis when performed; 1 view	**Diagnostic Procedures File**	Replaces deleted code 73510 (Radiologic examination, hip, unilateral; complete, minimum of 2 views), which was diagnsotic
73502	2 - 3 views	**Diagnostic Procedures File**	See 73501
73503	minimum of 4 views	**Diagnostic Procedures File**	See 73501
73521	Radiologic examination, hips, bilateral, with pelvis when performed; 2 views	**Diagnostic Procedures File**	Replaces deleted code 73520 (Radiologic examination, hips, bilateral, minimum of 2 views of each hip, including anteroposterior view of pelvis) which was diagnostic
73522	3-4 views	**Diagnostic Procedures File**	See 73521
73523	minimum of 5 views	**Diagnostic Procedures File**	See 73521
73551	Radiologic examination, femur; 1 view	**Diagnostic Procedures File**	Replaces deleted code 73550 (Radiologic examination, femur, 2 views) which was diagnostic
73552	minimum 2 views	**Diagnostic Procedures File**	see 73552
77767	Remote afterloading high dose rate radionuclide skin surface brachytherapy, includes basic dosimetry, when performed, lesion diameter up to 2.0 cm or 1 channel	**Services Recommended for Non-Coverage Table**	Discussed at October 2015 VBBS meeting
77768	Lesion diameter over 2.0 cm or 2 or more channels, or multiple lesions	**Services Recommended for Non-Coverage Table**	Discussed at October 2015 VBBS meeting

Code	Code description	Proposed Line	Comments
77770	Remote afterloading high dose rate radionuclide interstitial or intracavitary brachytherapy, includes basic dosimetry, when performed; 1 channel	**130** BENIGN NEOPLASM OF THE BRAIN AND SPINAL CORD **137** CANCER OF CERVIX **161** CANCER OF COLON, RECTUM, SMALL INTESTINE AND ANUS **195** CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER **204** CANCER OF SOFT TISSUE **213** CANCER OF UTERUS **263** CANCER OF PENIS AND OTHER MALE GENITAL ORGANS **266** CANCER OF RETROPERITONEUM, PERITONEUM, OMENTUM AND MESENTERY **267** CANCER OF LUNG, BRONCHUS, PLEURA, TRACHEA, MEDIASTINUM AND OTHER RESPIRATORY ORGANS **275** CANCER OF BLADDER AND URETER **291** CANCER OF VAGINA, VULVA, AND OTHER FEMALE GENITAL ORGANS **292** CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX **299** CANCER OF BRAIN AND NERVOUS SYSTEM **319** CANCER OF ESOPHAGUS **334** CANCER OF PROSTATE GLAND **377** BENIGN NEOPLASM OF RESPIRATORY AND INTRATHORACIC ORGANS **595** SECONDARY AND ILL-DEFINED MALIGNANT NEOPLASMS	Replaces deleted codes 77785-77787 (Remote afterloading high dose rate radionuclide brachytherapy) which were on lines 130,137,161,195,204,213,263,266, 267, 275, 291, 292, 299, 319, 334, 377, 595

Code	Code description	Proposed Line	Comments
77771	2-12 channels	**130** BENIGN NEOPLASM OF THE BRAIN AND SPINAL CORD **137** CANCER OF CERVIX **161** CANCER OF COLON, RECTUM, SMALL INTESTINE AND ANUS **195** CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER **204** CANCER OF SOFT TISSUE **213** CANCER OF UTERUS **263** CANCER OF PENIS AND OTHER MALE GENITAL ORGANS **266** CANCER OF RETROPERITONEUM, PERITONEUM, OMENTUM AND MESENTERY **267** CANCER OF LUNG, BRONCHUS, PLEURA, TRACHEA, MEDIASTINUM AND OTHER RESPIRATORY ORGANS **275** CANCER OF BLADDER AND URETER **291** CANCER OF VAGINA, VULVA, AND OTHER FEMALE GENITAL ORGANS **292** CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX **299** CANCER OF BRAIN AND NERVOUS SYSTEM **319** CANCER OF ESOPHAGUS **334** CANCER OF PROSTATE GLAND **377** BENIGN NEOPLASM OF RESPIRATORY AND INTRATHORACIC ORGANS **595** SECONDARY AND ILL-DEFINED MALIGNANT NEOPLASMS	See 77770

Code	Code description	Proposed Line	Comments
77772	over 12 channels	**130** BENIGN NEOPLASM OF THE BRAIN AND SPINAL CORD **137** CANCER OF CERVIX **161** CANCER OF COLON, RECTUM, SMALL INTESTINE AND ANUS **195** CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER **204** CANCER OF SOFT TISSUE **213** CANCER OF UTERUS **263** CANCER OF PENIS AND OTHER MALE GENITAL ORGANS **266** CANCER OF RETROPERITONEUM, PERITONEUM, OMENTUM AND MESENTERY **267** CANCER OF LUNG, BRONCHUS, PLEURA, TRACHEA, MEDIASTINUM AND OTHER RESPIRATORY ORGANS **275** CANCER OF BLADDER AND URETER **291** CANCER OF VAGINA, VULVA, AND OTHER FEMALE GENITAL ORGANS **292** CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX **299** CANCER OF BRAIN AND NERVOUS SYSTEM **319** CANCER OF ESOPHAGUS **334** CANCER OF PROSTATE GLAND **377** BENIGN NEOPLASM OF RESPIRATORY AND INTRATHORACIC ORGANS **595** SECONDARY AND ILL-DEFINED MALIGNANT NEOPLASMS	See 77770

Code	Code description	Proposed Line	Comments
80081	Obstetrics panel (includes HIV testing) This panel must include the following: Blood count , complete (CBC) and automated differential WBC count (85025 or 85027 and 85009) OR Blood count, complete (CBC) and automated (85027) and appropriate manual differential WBC count (85007 or 85009) Hepatitis B surface antigen (HBsAg) (87340) HIV-1 antigen(s) , with HIV-1 and HIV-2 antibodies, single result (87389) Antibody , rubella (86762) Syphilis test, non-treponemal antibody; qualitative (eg, VDRL, RPR, ART) (86592) Antibody screen, RBC, each serum technique (86850) Blood typing, ABO (86900) AND Blood typing, Rh (D) (86901) (When syphilis screening is performed using a treponemal antibody approach [86780], do not use 80081. Use the individual codes for the tests performed in the Obstetric panel)	**1** PREGNANCY	
88350	Immunofluroescence, per specimen, each additional single antibody stain procedure (List separately in addition to code for primary procedure)	**Diagnostic Procedures File**	Similar to 88346 (Immunofluroescence, per specimen,initial single antibody stain procedure) which is Diagnostic
90625	Cholera vaccine, live adult dosage, 1 dose schedule, for oral use	**Services Recommended for Non-Coverage Table**	Travel vaccine. Similar code 90724 (Cholera vaccine for injectable use) is on the SNRC.
90620	Meningococcal recombinant protein and outer membrane vesicle vaccine, serogroup B (MenB), 2 dose schedule for intramuscular use	**3** PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS	

Code	Code description	Proposed Line	Comments
90621	Meningococcal recombinant lipoprotein vaccine, serogroup B (MenB), 3 dose schedule, for intramuscular use	**3** PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS	
96931	Reflection confocal microscopy (RCM) for cellular and sub-cellular imaging of skin ; image acquisition and interpretation and report, , first lesion	**Services Recommended for Non-Coverage Table**	Discussed at October 2015 VBBS meeting
96932	image acquisition only, first lesion	**Services Recommended for Non-Coverage Table**	Discussed at October 2015 VBBS meeting
96933	interpretation and report only, first lesion	**Services Recommended for Non-Coverage Table**	Discussed at October 2015 VBBS meeting
96934	image acquisition and interpretation and report, each additional lesion (List separately in addition to code for primary procedure)	**Services Recommended for Non-Coverage Table**	Discussed at October 2015 VBBS meeting
96935	image acquisition only, each additional lesion (List separately in addition to code for primary procedure)	**Services Recommended for Non-Coverage Table**	Discussed at October 2015 VBBS meeting

Paravertebral Blocks

CPT codes:
64461 Paravertebral block (PVB) (paraspinous block), thoracic; single injection site
64462 second and any additional injection site(s)
64463 continuous infusion by catheter

Issue: Paravertebral nerve blocks are indicated for surgical procedures requiring unilateral analgesia or anesthesia. Common cases benefitting from unilateral paravertebral blocks are breast surgery, thoracotomy, herniorrhaphy, open cholecystectomy, and open nephrectomy. Bilateral paravertebral blocks can be a viable option for midline abdominal surgery.
The clinician may consider thoracic paravertebral blockade over thoracic epidural analgesia in patients for whom bilateral sympathectomy and subsequent hypotension would be especially detrimental. For example, the use of thoracic paravertebral blockade in a patient with severe aortic stenosis has been reported. In another study, thoracic paravertebral blockade resulted in more stable hemodynamics and equivalent analgesia when compared to thoracic epidural analgesia in thorocotomy patients. However, because bilateral spread can occur , this may cause hemodynamic compromise similar to epidural blockade.

The new CPT codes were developed to differentiate the paravertebral block from the transforaminal epidural (CPT 64479-64484), which are used to treat back pain and are currently on the Services Recommended for Non-Coverage.

Ancillary Guideline A1 governs coverage of nerve blocks.

HERC staff recommendations:

1) Recommend that HSD place CPT 64461-64463 (paravertebral blocks) on the Ancillary File
    a. Anesthesia codes are traditionally Ancillary
2) Modify Ancillary Guideline A1 as shown below

ANCILLARY GUIDELINE A1, NERVE BLOCKS

The Health Evidence Review Commission intends that single injection and continuous nerve blocks (CPT 64400-64450, 64461-64463) should be covered services if they are required for successful completion of perioperative pain control for, or post-operative recovery from a covered operative procedure when the diagnosis requiring the operative procedure is also covered. Additionally, nerve blocks are covered services for patients hospitalized with trauma, cancer, or intractable pain conditions, if the underlying condition is a covered diagnosis.

Endobronchial Ultrasound (EBUS)

CPT codes:

31652 (Bronchoscopy with endobronchial ultrasound (EBUS) guided transtracheal and/or transbronchial sampling (eg, aspiration[s]/biopsy[ies]), one or two mediastinal and/or hilar lymph node stations or structures
31653: 3 or more mediastinal and/or hilar lymph node stations or structures
31654: Bronchoscopy with transendoscopic endobronchial ultrasound (EBUS) during bronchoscopic diagnostic or therapeutic intervention(s) for peripheral lesion(s)

Issue: CPT 31652-31654 are replacing 31620 (Endobronchial ultrasound (EBUS) during bronchoscopic diagnostic or therapeutic intervention(s)). 31620 was reviewed in 2004 as a new code by the HSC and excluded as the oncologist then on the Commission felt that the lymph nodes would be biopsied anyway, and the ultrasound did not add to the diagnostic work up.

Since the 2004 review, there have been several meta-analyses published showing improved diagnostic accuracy with EBUS. New NCCN and NICE practice guidelines include the use of EBUS.

Evidence/other policies

1) **NCCN 2015** Clinical Practice Guideline Non-Small Cell Lung Cancer :
    a. Diagnostic tools that provide important additional strategies for biopsy include: endobronchial ultrasound (EBUS) guided biopsy
2) **NICE 2011** guidance on lung cancer **(study not included due to length)**:
    a. For diagnosis and staging
        i. Offer PET-CT, or EBUS-guided transbronchial needle aspiration (TBNA), or endoscopic ultrasound-guided fine needle aspiration (EUS-guided FNA), or non-ultrasound-guided TBNA as the first test for patients with an **intermediate probability of mediastinal malignancy** (lymph nodes between 10 and 20 mm maximum short axis on CT) who are potentially suitable for treatment with curative intent
        ii. Offer EBUS-guided TBNA for biopsy of paratracheal and peri-bronchial intraparenchymal lung lesions.
        iii. Offer neck ultrasound with sampling of visible lymph nodes or non-ultrasound-guided TBNA to patients with a **high probability of mediastinal malignancy** (lymph nodes > 20 mm maximum short axis on CT). If neck ultrasound is negative, follow with non-ultrasound-guided TBNA, EBUS-guided TBNA or EUS-guided FNA. If non-ultrasound-guided TBNA is negative, follow with EBUS-guided TBNA or EUS-guided FNA.
        iv. Consider combined EBUS and EUS for initial staging of the mediastinum as an alternative to surgical staging.
        v. Confirm negative results obtained by non-ultrasound-guided TBNA using EBUS-guided TBNA, EUS-guided FNA or surgical staging.
        vi. Every cancer network should have at least one centre with EBUS and/or EUS to ensure timely access.

Endobronchial Ultrasound (EBUS)

HERC staff recommendation:

1) Place CPT 31652-31654 (Bronchoscopy with endobronchial ultrasound (EBUS)) on Diagnostic Procedures File
    a. NCCN and NICE lists this procedure as useful in assisting biopsy for diagnosis

Sclerotherapy of Fluid Collections

CPT code:

49185 Sclerotherapy of a fluid collection (eg, lymphocele, cyst, or seroma), percutaneous, including contrast injection(s) sclerosant injection(s), diagnostic study, imaging guidance (eg, ultrasound, fluoroscopy) and radiological supervision and interpretation when performed

Issue: Sclerotherapy of fluid collections is a code for a procedure not previously reviewed for the Prioritized List. Sclerotherapy codes for varicose veins (CPT 36468-36471), esophageal varices (CPT 43204, 43243) and hemorrhoids (CPT 46500) are included on the Prioritized List. Sclerotherapy for cysts or other fluid collections involves inserting a needle into the fluid cavity, draining the fluid and then injecting a caustic agent such as ethanol or minocycline to cause the cavity to scar closed. Cysts and other fluid cavities may require treatment if they enlarge and cause pain or dysfunction or cause bleeding, infection, or organ torsion. Sclerosis is most commonly done with hepatic and renal cysts.

Cheng 2012 reviewed sclerotherapy for treatment of hepatic and renal cysts, and lymphoceles and finds this therapy to be effective for these conditions when they are symptomatic. **Lohela 2002** reviewed sclerotherapy for hepatic and renal cysts, thyroid and parathyroid cysts, pleural cysts, and hydroceles and found the therapy to be effective.

Sclerotherapy of Fluid Collections

The following table contains diagnoses included in the Cheng and Lohela reviews. Note: cyst diagnoses are found on more than the lines below, depending on the organ involved.

ICD-10 Code	Code Description	Line(s)
E04.1	Nontoxic single thyroid nodule (includes thyroid cyst) Note: ICD-9 (246.2 Cysts of thyroid) equivalent is on line 634 CYST, HEMORRHAGE, AND INFARCTION OF THYROID	**656** ENDOCRINE AND METABOLIC CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
E21.4	Other specified disorders of parathyroid gland (includes parathyroid cysts)	**229** DISORDERS OF PARATHYROID GLAND; BENIGN NEOPLASM OF PARATHYROID GLAND; DISORDERS OF CALCIUM METABOLISM
I89.8	Other specified noninfective disorders of lymphatic vessels and lymph nodes (includes lymphocele)	**427** LYMPHEDEMA
J94.8	Other specified pleural conditions (includes pleural cysts)	**569** PLEURISY
K76.89	Other specified diseases of liver (includes liver cysts)	**298** ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER
M67.4x	Ganglion	**596** GANGLION
M70.8xx and M70.9xx	Other and unspecified soft tissue disorders related to use, overuse and pressure (includes non-postoperative seromas)	**607** DISORDERS OF SOFT TISSUE
N21.8	Cyst of kidney, acquired	**559** CYST OF KIDNEY, ACQUIRED
N43.3	Hydrocele, unspecified Note: on line 172 for surgical excision/repair as pediatric urology considers similar to hernia in children	**172** COMPLICATED HERNIAS; UNCOMPLICATED INGUINAL HERNIA IN CHILDREN AGE 18 AND UNDER; PERSISTENT HYDROCELE **547** HYDROCELE
N60.0x	Solitary cyst of breast	**484** BREAST CYSTS AND OTHER DISORDERS OF THE BREAST
T88.8xx	Other specified complications of surgical and medical care, not elsewhere classified (includes surgical seromas) NOTE: 998.13 (Seroma complicating a procedure) is on 428 COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT	Diagnostic Workup File

Sclerotherapy of Fluid Collections

HERC staff recommendation:

1) Add ICD-10 T88.8xx (Other specified complications of surgical and medical care, not elsewhere classified) to line **428** COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT
    a. Advise HSD to remove T88.8xx from the Diagnostic Workup File
2) Move E04.1 (Nontoxic single thyroid nodule) from line **656** ENDOCRINE AND METABOLIC CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY to line **634** CYST, HEMORRHAGE, AND INFARCTION OF THYROID
3) Place CPT 49185 (Sclerotherapy of a fluid collection (eg, lymphocele, cyst, or seroma), percutaneous, including contrast injection(s) sclerosant injection(s), diagnostic study, imaging guidance (eg, ultrasound, fluoroscopy) and radiological supervision and interpretation when performed) on the following lines
    a. **229** DISORDERS OF PARATHYROID GLAND; BENIGN NEOPLASM OF PARATHYROID GLAND; DISORDERS OF CALCIUM METABOLISM
    b. **298** ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER
    c. **427** LYMPHEDEMA
    d. **428** COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT
    e. **484** BREAST CYSTS AND OTHER DISORDERS OF THE BREAST
    f. **547** HYDROCELE
    g. **559** CYST OF KIDNEY, ACQUIRED
    h. **569** PLEURISY
    i. **596** GANGLION
    j. **607** DISORDERS OF SOFT TISSUE
    k. **634** CYST, HEMORRHAGE, AND INFARCTION OF THYROID
4) Adopt a new guideline note as shown below
5) Alternate: add CPT 49185 to the Ancillary List with an Ancillary Guideline similar to the one shown below.

GUIDELINE NOTE XXX, SCLEROTHERAPY OF FLUID COLLECTIONS

Lines 172, 229, 298, 427, 428, 484, 547, 559, 569, 596, 607, 634

Sclerotherapy for fluid collections (CPT 49185) is included on these lines only for the treatment of cysts, seromas or lymphoceles which are causing bleeding, infection, severe pain, organ torsion, or organ dysfunction.

Percutaneous Sclerotherapy of Cystic Lesions

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Abstract

With modern cross-sectional imaging techniques, cystic lesions are very common and usually incidental findings, especially if small. However, when cysts enlarge, become infected, bleed, or undergo torsion, they can be symptomatic, and percutaneous drainage can be effective in the management. When cysts recur after aspiration, which is often the case for hepatic and renal cysts, cyst sclerosis or surgical unroofing may be required. This article describes the indications for and technical aspects of percutaneous sclerotherapy of cystic lesions of multiple organ systems.

Keywords

- interventional radiology
- sclerotherapy
- cysts
- alcohol

Objectives: Upon completion of this article, the reader should be able to describe the patient population for whom sclerotherapy of cystic lesions is most appropriate, and the technique used during such procedures.

Accreditation: Tufts University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit: Tufts University School of Medicine designates this journal-based CME activity for a maximum of ***1 AMA PRA Category 1 Credit***™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Cystic lesions can be characterized as either congenital or acquired. From a histologic perspective, cystic lesions are classified as true cysts, containing epithelium or endothelium, or pseudocysts. They can occur sporadically or as part of syndromes such as Von Hippel-Lindau or autosomal dominant polycystic kidney disease. Additionally, acquired cysts can result from trauma or infection. They can be found in essentially every solid organ in the body but most commonly affect the liver, pancreas, kidney, and ovary. Some authors extend the definition of cystic lesions to postoperative collections such as lymphoceles, hematomas, seromas, peritoneal inclusion cysts, urinomas, and bilomas.

With modern cross-sectional imaging techniques, cystic lesions are very common and usually incidental findings, especially if small. However, when cysts enlarge, become infected, bleed, or undergo torsion, they can be symptomatic, and percutaneous drainage can be effective in the management.[1] When cysts recur after aspiration, which is often the case for hepatic and renal cysts,[2] cyst sclerosis or surgical unroofing may be required.

General Principles of Sclerotherapy

Patients with symptomatic cysts should be referred for imaging. The chosen modality usually depends on the location of the cysts. Ultrasound is fast and readily available, and due to lack of radiation is usually used first. Ultrasound is also usually preferred in certain situations, such as in the evaluation of ovarian cysts or more superficial postoperative lymphoceles. Magnetic resonance imaging may be better at identifying the organ of origin for deep pelvic cysts. Simple cysts are typically dark on T1-weighed images and bright on T2-weighted images. However, these signals undergo changes if the cysts are proteinaceous or hemorrhagic. Contrast-enhanced computed tomography (CT) can detect solid organ cysts and cysts in other locations well. Simple cysts in general have a thin wall without mural thickening or nodularity.

Therapeutic options for cystic lesions include surgical resection or unroofing, percutaneous aspiration, percutaneous drainage, and sclerotherapy. Surgery, despite its higher morbidity and the added risk associated with anesthesia, is used in cases when there is no safe percutaneous window, when percutaneous treatment has failed, or in certain cysts located in the liver (surgical unroofing or laparoscopic fenestration) and pancreas (surgical marsupialization).

Issue Theme Biopsies and Drains; Guest Editor, Jonathan M. Lorenz, MD, FSIR

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Ultrasound-guided drainages and sclerotherapy

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Abstract Ultrasonically guided fluid collection and abscess drainage have become routine procedures in various parts of the body. In most cases ultrasound is the only imaging and guidance modality needed; however, it is of the utmost importance to remember that CT and fluoroscopy with contrast often give invaluable information when the true extent of the process has to be determined and when assessing the safest route for the catheter in anatomically complicated areas. The importance of irrigation of the abscess cavity with fluids and the ready use of urokinase should be emphasized. Ethanol sclerotherapy is a simple and safe procedure to treat symptomatic hepatic or renal cysts. Parathyroid adenomas and cysts, as well as thyroid cysts, can also be treated with ethanol sclerotherapy in selected cases. Purified mineral talc has been used in pleurodesis and hydrocele sclerotherapy, whereas doxycycline or ethanol is used for postoperative lymphoceles. Both abscess drainages and sclerotherapy procedures are minimally invasive, simple, safe, inexpensive and reasonably efficacious treatment in many clinical instances and may be at least an alternative to surgical treatment, often offering significant advantages over surgery.

Keywords Drainage · Sclerotherapy · Ultrasound · Abscess · Interventional procedures

Introduction

Ultrasonically guided drainage is usually the simplest way to treat abscess or fluid collections [1, 2]; however, CT fluoroscopy offers the localization advantages of CT with improved procedure time, and facilitates effective performance of percutaneous abdominal and pelvic interventional procedures in anatomically difficult areas, such as pancreas, or in multilocular abscesses or pleural empyemas. [3, 4]. Conventional fluoroscopy with injection of contrast medium via the drainage catheter is also useful in assessing the true extent of the inflammatory process. Color power Doppler is useful when determining safe access route for the puncture needle or catheter to avoid great vessels, and to detect aneurysms and arteriovenous malformations.

Sclerotherapy is used to treat symptomatic hepatic, renal, chronic pleural effusions [5, 6], thyroid cysts, and for hydroceles, lymphoceles and for tissue-ablating purposes (i.e. metastasis, parathyroid adenomas).

Patient preparation for abscess drainages and sclerotherapy

Informing the patient and the staff of the clinical department and the cooperation of the patient is of utmost importance in interventional procedures [7]. The blood coagulation tests must be individualized. Simple aspiration procedures, such as thoracocentesis or ascites drainage, usually require no preliminary patient preparation or no coagulation tests. In general, only the clinical history for

CPT: **50705** Ureteral embolization or occlusion, including imaging guidance (eg, ultrasound and/or fluoroscopy)

Issue: This is a new type of treatment code. However, the use of this procedure has been reported in the literature for more than 30 years. It does not appear to be a procedure that would be likely to be abused or overused.

Previously, this procedure was coded with more generic arterial embolization CPT codes.

Ward 2010 reviewed the use of ureteral embolization, among other genitourinary embolization procedures. The reported uses for ureteral embolization were for urine leaks caused by vesicovaginal fistula, persistent urine leaks related to prior pelvic surgery, or persistent hematuria secondary to an unresectable malignancy. Excellent technical success rates with symptom resolution have been reported.

ICD-10 diagnosis codes related to the conditions reported in Ward 2010:

N82.0 (Vesicovaginal fistula) on line 235 URINARY FISTULA
C66.x (Malignant neoplasm of ureter) on Line 275 CANCER OF BLADDER AND URETER
T83.xx (variety of urinary tract complications) on line 290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT

The current CPT codes for arterial embolization (37241-37244) do not appear on lines 235, 275 or 290. CPT codes for embolization of tumors (37243 and 61624), and only appears on tumor lines 130 BENIGN NEOPLASM OF THE BRAIN AND SPINAL CORD, 320 CANCER OF LIVER and 409 UTERINE LEIOMYOMA AND POLYPS. There are currently no embolization codes for use for treatment of conditions such as urinary fistulas or urinary leakage.

HERC staff recommendation:

1) Place 50705 Ureteral embolization or occlusion, including imaging guidance (eg, ultrasound and/or fluoroscopy) on the Services Recommended for Non-Coverage
    a. Consistent with current similar code placement
    b. Each indication could be reviewed in detail for consideration for coverage in the future
    c. Alternate: place 50705 on lines 235 URINARY FISTULA, 275 CANCER OF BLADDER AND URETER, and 290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT

Transcatheter Therapeutic Embolization of Genitourinary Pathology

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With the advent of smaller vascular catheters and improved imaging techniques, percutaneous transcatheter embolization has become a valuable adjunct for the treatment of patients with various genitourinary pathologic conditions. Multiple embolic agents are now employed in an array of situations to devascularize organs, stop bleeding, and occlude passageways. [Rev Urol. *2000;2(4):236-245, 252*]

Key words: Embolization • Genitourinary tract • Nephrectomy • Occlusive therapy

Transcatheter embolization has a role in the management of renal cell carcinoma (RCC), renal trauma, ureteral occlusion, bladder hemorrhage, pelvic bleeding following trauma or surgery, correction of internal spermatic vein varicoceles, and high-flow arterial priapism. In this article, we briefly review the choices open to urologists and their patients and the materials available to interventional radiologists. Images detailing the treatment and anatomy in each case are provided.

Principles of Transcatheter Embolic Techniques

Multiple materials for the occlusion of vessels have been evaluated during the development of embolization techniques. The choice of an embolic material for a specific clinical situation depends on a variety of considerations: the size of the vessels or organ to be embolized, the size of the catheter that can be deployed to the target region, whether repeated embolization through a specific arterial or venous vasculature is anticipated, and whether temporary or permanent occlusion is desired.

Agents that offer temporary occlusion (days to weeks) with spontaneous dissolution are absorbable gelatin sponge, microfibrillar collagen, and autologous clot (Figure 1). The most commonly used agent, absorbable gelatin sponge (1C), is usually rolled into small, torpedo-shaped pieces and placed in a tuberculin syringe (1A). Multiple sponge rolls are then injected, with normal saline, directly into the vascular catheter, which has been positioned at the site of desired embolization.

Agents that provide permanent vascular occlusion are polyvinyl alcohol particles (1B), metal coils (1D), and detachable balloons. Liquid sclerosing agents are also extensively used to achieve permanent vascular occlusion. Their liquid state allows peripheral embolization well beyond the limits of the smallest available vas-

Intra-arterial Interventions for Acute Stroke

CPT code:

> **61645** Percutaneous arterial transluminal mechanical thrombectomy and/or infusion for thrombolysis, intracranial, any method, including diagnostic angiography, fluoroscopic guidance, catheter placement, and intraprocedural pharmacological thrombolytic injection(s)

Issue: Several new therapies for stroke have been developed and studied in the past decade which involve threading a catheter through the femoral artery to the affected artery in the brain. The stroke is then treated either by injecting thrombolytic medications directly into the affected artery or by removing a clot mechanically with or without placing a stent.

The standard of care for acute stroke remains the peripheral IV infusion of thrombolytics, except for those patients with a hemorrhagic stroke or with other contraindications to thrombolytic therapy.

Similar codes:
Previously, intracranial thrombectomy was coded with 37184 (Primary percutaneous transluminal mechanical thrombectomy, noncoronary, non-intracranial, arterial or arterial bypass graft, including fluoroscopic guidance and intraprocedural pharmacological thrombolytic injection(s); initial vessel) while intracranial thrombolysis was coded with 37211 (Transcatheter therapy, arterial infusion for thrombolysis other than coronary or intracranial, any method, including radiological supervision and interpretation, initial treatment day) [green wording is new for 2016]. 37184 has been modified for 2016 with the addition of "non-intracranial" while 37211 was has been modified for 2016 with "or intracranial." 37184 and 37211 are on lines 240 LIMB THREATENING VASCULAR DISEASE, INFECTIONS, AND VASCULAR COMPLICATIONS, 258 ARTERIAL EMBOLISM/ THROMBOSIS: ABDOMINAL AORTA, THORACIC AORTA, 354 NON-LIMB THREATENING PERIPHERAL VASCULAR DISEASE, 452 ATHEROSCLEROSIS, AORTIC AND RENAL.

Evidence

1) **NICE 2013,** review of mechanical clot retrieval for acute ischemic stroke
    a. Note: revision is currently underway, expected to be published in 2016
    b. The current evidence on mechanical clot retrieval for treating acute ischaemic stroke shows that efficacy is unproven. With regard to safety, there are risks of serious complications. The following recommendations balance these considerations against the poor prognosis of many patients with stroke. Suitability for thrombolysis can be guided by criteria used in the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) trial.
    c. Patients with acute ischaemic stroke for whom thrombolysis is unsuitable or has failed: The procedure should only be used with special arrangements for clinical governance, consent and audit or research.
    d. Patients with acute ischaemic stroke for whom thrombolysis is suitable: The procedure should only be used in the context of research

   e. Selection of patients for mechanical clot removal should be done by clinicians experienced in the use of thrombolysis for stroke. The procedure should be carried out in specialist centres by experienced interventional neuroradiologists with appropriate facilities and support

1) **AHRQ 2013,** evidence review for mechanical thrombectomy for the treatment of acute stroke
   a. Conclusions: Currently available neurothrombectomy devices offer intriguing treatment options in patients with acute ischemic stroke, although a paucity of high quality research currently exists. There remains a need for further research on the topic, including randomized controlled trials to determine the optimal device(s) to use, and the patient populations most likely to benefit from their use.
   b. Noted that 11 ongoing studies are examining the use of mechanical thrombectomy in stroke
2) **CTAF 2013,** review of thrombectomy for treatment of acute stroke **(PDF not included due to size)**
   a. There was no benefit to intraarterial therapy in any of the studies (compared to IV thrombolytics) including the subset of patients with significant amounts of potentially salvageable ischemic brain tissue seen on brain imaging prior to the intervention. All of the trials reported significant adverse events related to the intra-arterial procedure in a clinical important proportion of the treated patients.
   b. It is recommended that the use of the thrombectomy devices does not meet Technology Assessment Criteria 3 through 5 for safety, effectiveness and improvement in health outcomes when used to treat acute ischemic stroke.
   c. There was a note that the review was limited due to the majority of studies reviewed using older generation devices; early studies on newer generation devices were more promising

1) **Prabhakaran 2015**, systematic review of treatments for acute stroke
   a. Intravascular thrombolysis is the standard of care for patients presenting within 4.5 hours of onset of acute stroke
   b. No recommendation made for use of intra-arterial thrombolytics
      i. Reviewed one large trial of intra-arterial thrombolytics (PROACT II), which showed marginal benefit vs standard therapy, and the benefit was partially offset by the increased risk of harm
   c. Based on multiple randomized clinical trials, intra-arterial therapy using stent retrievers improves recanalization of proximal artery occlusions and clinical outcomes beyond that possible with IV rtPA or supportive care alone.
      i. Recommendation based on review of 4 large RCTs (MR CLEAN,ESCAPE, EXTEND I-A, and SOLITAIRE) which showed better functional outcomes for patients with mechanical stent removal compared to standard IV thrombolysis
2) **Wardlaw 2013**, Cochrane review of thrombolysis for treatment of acute stroke
   a. N=5 trials (N = 485) compared different routes of administration.

b. There was no evidence of any benefit for intra-arterial over intravenous treatment.
c. **Authors' conclusions** At present, intravenous rt-PA at 0.9mg/kg as licensed in many countries appears to represent best practice and other drugs, doses or routes of administration should only be used in randomised controlled trials.

Evidence based guidelines

1) **SIGN 2008,** guideline for the treatment of acute stroke (PDF not included due to size)
   a. Level C recommendation for mechanical thrombectomy
      i. Mechanical clot retrieval devices, when used by experienced interventional neuroradiologists, may be considered in patients who are ineligible for thrombolytic drug therapy or who have failed to improve clinically or recanalise following intravenous thrombolysis.
   b. No recommendation made regarding intra-arterial thrombolytic therapy

2) **NICE 2010,** guideline for the treatment of acute stroke (PDF not included due to size)
   a. Does not mention mechanical thrombectomy or intra-arterial thrombolytic therapy

3) **Jauch 2013,** AHA/ASA guidelines for treatment of acute stroke (PDF not included due to size)
   a. Patients eligible for intravenous rtPA should receive intravenous rtPA even if intra-arterial treatments are being considered *(Class I; Level of Evidence A)*.
   b. Intra-arterial fibrinolysis is beneficial for treatment of carefully selected patients with major ischemic strokes of <6 hours' duration caused by occlusions of the MCA who are not otherwise candidates for intravenous rtPA *(Class I; Level of Evidence B)*. The optimal dose of intra-arterial rtPA is not well established, and rtPA does not have FDA approval for intra-arterial use.
   c. As with intravenous fibrinolytic therapy, reduced time from symptom onset to reperfusion with intraarterial therapies is highly correlated with better clinical outcomes, and all efforts must be undertaken to minimize delays to definitive therapy *(Class I; Level of Evidence B)*.
   d. Intra-arterial treatment requires the patient to be at an experienced stroke center with rapid access to cerebral angiography and qualified interventionalists. An emphasis on expeditious assessment and treatment should be made. Facilities are encouraged to define criteria that can be used to credential individuals who can perform intra-arterial revascularization procedures. Outcomes on all patients should be tracked *(Class I; Level of Evidence C)*.
   e. When mechanical thrombectomy is pursued, stent retrievers such as Solitaire FR and Trevo are generally preferred to coil retrievers such as Merci *(Class I; Level of Evidence A)*. The relative effectiveness of the Penumbra System versus stent retrievers is not yet characterized.
   f. The Merci, Penumbra System, Solitaire FR, and Trevo thrombectomy devices can be useful in achieving recanalization alone or in combination with pharmacological fibrinolysis in carefully selected patients *(Class IIa; Level of*

Evidence B). Their ability to improve patient outcomes has not yet been established. These devices should continue to be studied in randomized controlled trials to determine the efficacy of such treatments in improving patient outcomes.

g. Intra-arterial fibrinolysis or mechanical thrombectomy is reasonable in patients who have contraindications to the use of intravenous fibrinolysis *(Class IIa; Level of Evidence C)*.
h. Rescue intra-arterial fibrinolysis or mechanical thrombectomy may be reasonable approaches to recanalization in patients with large-artery occlusion who have not responded to intravenous fibrinolysis. Additional randomized trial data are needed *(Class IIb; Level of Evidence B)*.
i. The usefulness of mechanical thrombectomy devices other than the Merci retriever, the Penumbra System, Solitaire FR, and Trevo is not well established *(Class IIb; Level of Evidence C)*. These devices should be used in the setting of clinical trials.
j. The usefulness of emergent intracranial angioplasty and/or stenting is not well established. These procedures should be used in the setting of clinical trials *(Class IIb; Level of Evidence C)*.

HERC staff recommendations:

1) Place CPT **61645** (Percutaneous arterial transluminal mechanical thrombectomy and/or infusion for thrombolysis, intracranial , any method, including diagnostic angiography, fluoroscopic guidance, catheter placement, and intraprocedural pharmacological thrombolytic injection(s)) on the **Services Recommended for Non-Coverage Table** as investigational
    a. Intra-arterial thrombolysis generally has not been found to have evidence for effectiveness
    b. Mechanical thrombectomy has generally not been found to have high level evidence of effectiveness in our trusted sources (ie NICE and AHRQ), but has recommendations for use among expert guidelines. This technology appears to be an active area of research and new generation devices, particularly utilizing stents after thrombectomy, appear to be much more promising.
    c. CPT codes currently used for these procedures (37184 and 37211) are not included on the stroke line (322) or other intracranial disease line
2) Plan to review this technology either through VBBS or through HTAS in the near future given the rapidly evolving field and expected trusted sources guideline revisions
3) HERC staff will review intra-arterial balloon angioplasty (CPT 61630) and intravascular stenting (CPT 61635) of intracranial vessels in the near future or will have these reviewed by HTAS during the review in #2 above. These procedures are currently on line 200 SUBARACHNOID AND INTRACEREBRAL HEMORRHAGE/HEMATOMA; CEREBRAL ANEURYSM; COMPRESSION OF BRAIN. These procedures are not recommended for coverage by NICE; a fuller evidence review needs to be conducted

NICE guidance

Mechanical clot retrieval for treating acute ischaemic stroke

Interventional procedure guidance
Published: 23 July 2013
nice.org.uk/guidance/ipg458

1 Guidance

The current evidence on mechanical clot retrieval for treating acute ischaemic stroke shows that efficacy is unproven. With regard to safety, there are risks of serious complications. The following recommendations balance these considerations against the poor prognosis of many patients with stroke. Suitability for thrombolysis can be guided by criteria used in the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) trial.

1.1 **Patients with acute ischaemic stroke for whom thrombolysis is unsuitable or has failed:** The procedure should only be used with special arrangements for clinical governance, consent and audit or research. Clinicians wishing to use mechanical clot retrieval for treating acute ischaemic stroke in these patients should take the following actions:

- Inform the clinical governance leads in their Trusts.
- Ensure that patients (and when appropriate their relatives or carers) understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, the use of NICE's information for the public is recommended.
- Submit details of all patients to the Safe Implementation of Treatments in Stroke Thrombectomy (SITS-TBY) register.

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- NICE encourages prospective studies of mechanical clot retrieval in these patients, including comparison of outcomes against those of patients who do not have the procedure. These studies should report details of patient selection, timing of the intervention after onset of symptoms, the devices and techniques used, and functional outcomes.

1.2 **Patients with acute ischaemic stroke for whom thrombolysis is suitable:** The procedure should only be used in the context of research:

- Research should include randomised studies comparing mechanical clot retrieval against thrombolysis or other current methods of management and should report details of patient selection, timing of the intervention after onset of symptoms, the devices and techniques used, complications and functional outcomes.
- NICE encourages clinicians to enter patients into randomised trials such as the PISTE trial. In addition, details of all patients should be entered into the SITS-TBY register.

1.3 Selection of patients for mechanical clot removal should be done by clinicians experienced in the use of thrombolysis for stroke. The procedure should be carried out in specialist centres by experienced interventional neuroradiologists with appropriate facilities and support.

2 The procedure

2.1 Indications and current treatments

2.1.1 Acute ischaemic stroke refers to stroke caused by arterial thrombosis or embolism. This results in loss of neurological function, leading to symptoms such as numbness or weakness of the face, arm or leg on one side of the body, and often problems with speech and swallowing.

2.1.2 Rapid assessment and early intervention, typically by thrombolysis, can limit ischaemic damage to brain cells. Mechanical clot retrieval is used for treating occlusions of large vessels.

2.2 Outline of the procedure

2.2.1 Mechanical clot retrieval for treating acute ischaemic stroke is carried out with the patient under sedation with local anaesthesia or general anaesthesia.

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Patients first undergo conventional cerebral angiography to demonstrate the presence and location of arterial occlusion. A delivery catheter is inserted, usually through the femoral artery at the groin, and advanced using X-ray guidance to the occluded artery. A clot retrieval device attached to a guidewire is introduced through the delivery catheter to the site of the occlusion. Several types of device and different techniques have been used for clot retrieval, including looped or corkscrew-like devices, snares or micro-forceps, and suction devices. In current practice, stent retrievers are the most commonly used type of device.

2.2.2 The aim is to perform the procedure as soon as possible, within a few hours after the onset of stroke symptoms.

> Sections 2.3 and 2.4 describe efficacy and safety outcomes from the published literature that the Committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see the overview.

2.3 Efficacy

The efficacy outcomes described below include death occurring more than 30 days after the procedure. Deaths occurring within 30 days or as a result of intracranial haemorrhage are reported as safety outcomes.

2.3.1 A meta-analysis of 1113 patients reported complete recanalisation in 41% of the 580 patients for whom data were available (absolute number not reported). A meta-analysis of 147 patients reported successful flow restoration in 71% (104/147) of patients. A systematic review of 262 patients reported successful recanalisation in 90% (235/262) of patients.

2.3.2 A randomised controlled trial (RCT) of 113 patients reported successful recanalisation without symptomatic intracranial haemorrhage in 61% (34/56) of patients treated by a stent retriever and 24% (13/54) of patients treated by a coil retrieval device. A case series of 141 patients (74 received intravenous recombinant tissue plasminogen activator [rtPA] plus mechanical thrombectomy) reported successful revascularisation (defined as modified thrombosis in cerebral infarction [mTICI] scores 2b or 3) in 85% (120/142) of arterial occlusions.

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2.3.3 The meta-analyses of observational or interventional studies of 1113 and 147 patients reported a favourable outcome (90-day modified Rankin scale (mRS) score of 2 or under) in 40% of patients for whom data were available (961 patients; absolute number not reported) and 33% (49/146) of patients respectively. The systematic review of 262 patients reported an mRS of 2 or under in 51% (133/262) of patients (1 to 3 months after the procedure), with improvements of at least 10 points in the National Institutes of Health Stroke scale (NIHSS) in 52% (102/196) of patients (reported as 'immediate to 3 months' after the procedure).

2.3.4 In an RCT of 656 patients comparing endovascular therapy (n=434) against intravenous tissue plasminogen activator (tPA) alone (n=222), there was no significant difference in the number of patients with an mRS of 2 or under (indicating functional independence) at 90 days (41% for endovascular therapy compared with 39% for intravenous tPA). A case series of 223 patients reported that endovascular therapy (n=123, including mechanical thrombectomy [25% of patients], intra-arterial thrombolysis with rtPA [35% of patients] or both [40% of patients]) was significantly associated with a favourable outcome (defined as an mRS of 2 or under) at 90 days, compared with intravenous thrombolysis (odds ratio 4 [95% confidence interval 1.8 to 9; p=0.0004]).

2.3.5 The meta-analysis of 1113 patients reported a pooled mortality rate of 28% in patients for whom data were available (n=952; absolute number not reported; $p<0.0001$; $I^2=60\%$; follow-up not reported). The meta-analysis of 147 patients reported an overall 90-day mortality rate of 31% (45/147; level of significance not stated) with rates of 29% (37/126) for patients with clots accessible by a mechanical retrieval device, compared with 38% (8/21) for patients with inaccessible clots. The case series of 141 patients reported death within 90 days in 24% (16/67) of patients who were treated by mechanical clot retrieval alone and in 18% (13/74) of patients who were treated by mechanical clot retrieval and intravenous rtPA. Causes included stroke, cardiac events, pulmonary disease and renal failure.

2.3.6 The Specialist Advisers listed key efficacy outcomes as successful device deployment, clot retrieval, angiographic recanalisation of the occluded vessel (for example assessed by TIMI/TICI [thrombolysis in myocardial infarction/ thrombolysis in cerebral ischaemia] score), time to recanalisation, clinical recovery, NIHSS before and after the procedure, mRS score at follow-up, and

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reduction in death rates and long-term dependency. One of the specialist advisers stated that efficacy should be related to clinical outcome and not technical success of the procedure.

2.4 Safety

2.4.1 Death within 7 days was reported in 12% (52/434) of patients treated by endovascular therapy and in 11% (24/222) of patients treated by intravenous tPA in the RCT of 656 patients; this difference was not significant.

2.4.2 Death (within 7 days) as a result of intracranial haemorrhage was reported in 2% (4/181) of patients treated by endovascular treatment and less than 1% (1/181) of patients treated by intravenous tPA in an RCT of 362 patients.

2.4.3 Distal emboli in a new territory was reported in 2% (1/58) of patients treated by a stent retriever and 6% (3/55) of patients treated by a coil retrieval device in the RCT of 113 patients. Embolisation to a previously uninvolved territory was reported in 7% (6/88) of patients treated by a stent retriever and 4% (4/90) of patients treated by a coil retrieval device in an RCT of 178 patients. Re-occlusion of the target vessel during the procedure was reported in 2% (3/125) of patients in a case series of 125 patients. Re-occlusions or distal occlusions were described in 5 patients included in the US Food and Drug Administration's Manufacturer and User Facility Device Experience (MAUDE) database, 1 of whom died as a result.

2.4.4 Air embolism was reported in 1 patient in each of the stent retriever and coil retrieval device treatment groups in the RCT of 113 patients (timing not reported).

2.4.5 Symptomatic intracranial haemorrhage was reported in 8% of patients for whom data were available (n=983; absolute number and follow-up not reported) in the meta-analysis of 1113 patients. Symptomatic haemorrhagic complications were reported in 7% (16/236) of patients in the systematic review of 262 patients (timing not reported). There were 5 procedure-induced subarachnoid haemorrhages in the systematic review of 262 patients.

2.4.6 Symptomatic intracranial haemorrhage (as defined in the European Cooperative Acute Stroke Study [ECASS] III), was reported in 7% (6/88) of patients treated

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by a stent retriever and 9% (8/90) of patients treated by a coil retrieval device in the RCT of 178 patients. Symptomatic intracerebral haemorrhage (within 30 hours) was reported in 6% (27/434) of patients treated by endovascular therapy compared with 6% (13/222) of patients treated by intravenous rtPA in the RCT of 656 patients. Asymptomatic haemorrhage (within 30 hours) was reported in 27% (119/434) of patients treated by endovascular therapy compared with 19% (42/222) of patients treated by intravenous rtPA (p=0.01) in this RCT. Symptomatic intracranial haemorrhage (within 24 hours of the procedure; defined as parenchymal haematoma type 2 with neurological worsening on NIHSS or leading to death) was reported in 3% (2/66) of patients treated by mechanical clot retrieval with intravenous rtPA and 5% (3/58) of patients treated by mechanical clot retrieval alone in the case series of 141 patients.

2.4.7 Access site complications needing surgical repair or blood transfusion were reported in 2% (2/88) of patients treated by a stent retriever and 1% (1/90) of patients treated by a coil retrieval device in the RCT of 178 patients.

2.4.8 Non-specific haemorrhage and subarachnoid haemorrhage were each reported in 5 patients included in the MAUDE database. There was 1 death after non-specific haemorrhage and 3 deaths after subarachnoid haemorrhage.

2.4.9 Clinically significant groin haemorrhages that needed surgical repair were reported in 2% (3/141) of patients in a case series of 151 patients.

2.4.10 Intramural arterial dissection was reported in 1% (1/90) of patients treated by a coil retrieval device in the RCT of 178 patients. Vessel dissection was reported in 3% (2/58) of patients treated by a stent retriever and in 2% (1/55) of patients treated by a coil retrieval device in the RCT of 113 patients. Vessel dissection was reported in 1% (2/141) of patients in the case series of 141 patients treated by mechanical clot retrieval (alone or with rtPA). Dissections occurred in 3 patients included in the MAUDE database.

2.4.11 Vessel perforation was reported in 1% (1/88) and 2% (1/58) of patients treated by a stent retriever, and in 10% (9/90) and 6% (3/55) of patients treated by a coil retrieval device in the RCTs of 178 patients and 113 patients, respectively.

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2.4.12 There were 2 incidences of self-detachments of the stent retriever, 1 entanglement of the stent retriever and 1 in-stent thrombosis reported in the systematic review of 262 patients. Device separation was reported in 2% (1/58) of patients treated by a stent retriever in the RCT of 113 patients. Device fractures occurred in 3% (11/341) of clot retrieval devices used in the case series of 151 patients. In 2 of these patients device fracture was reported as likely to have contributed to the patient's death.

2.4.13 In addition to the above, the Specialist Advisers listed myocardial infarction, anaphylaxis, exsanguination, contrast reactions, anaesthetic complications and reperfusion cerebral oedema as theoretical adverse events.

2.5 Other comments

2.5.1 The Committee noted that the prognosis for patients with large vessel occlusion(s) for whom thrombolysis is considered unsuitable or has failed is very poor and this underpinned the recommendation in 1.1.

2.5.2 The Committee noted the substantial amount of reported data on the technical success of mechanical clot retrieval for acute ischaemic stroke in contrast to the small volume of data relating to clinical outcomes in the context of the natural history of stroke.

2.5.3 The Committee noted that a range of devices and techniques can be used for this procedure, that the technology is evolving, and that there is evidence of significantly different associated outcomes. This made interpretation of the evidence difficult.

3 Further information

3.1 For related NICE guidance see the NICE website.

Information for patients

NICE has produced information on this procedure for patients and carers (Information for the public). It explains the nature of the procedure and the guidance issued by NICE, and has been written with patient consent in mind.

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Changes after publication

April 2014: Minor maintenance

About this guidance

NICE interventional procedure guidance makes recommendations on the safety and efficacy of the procedure. It does not cover whether or not the NHS should fund a procedure. Funding decisions are taken by local NHS bodies after considering the clinical effectiveness of the procedure and whether it represents value for money for the NHS. It is for healthcare professionals and people using the NHS in England, Wales, Scotland and Northern Ireland, and is endorsed by Healthcare Improvement Scotland for implementation by NHSScotland.

This guidance was developed using the NICE interventional procedures guidance process.

We have produced a summary of this guidance for patients and carers.

Your responsibility
This guidance represents the views of NICE and was arrived at after careful consideration of the available evidence. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of healthcare professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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Accreditation



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Technical Brief Number 4

Effective Health Care Program

Neurothrombectomy Devices for Treatment of Acute Ischemic Stroke

Executive Summary

Background

Acute ischemic strokes are associated with poor outcomes and high health care burden. In patients with occlusions of large cerebral vessels, patients with high baseline stroke severity scores as defined by the National Institute of Health Stroke Score (NIHSS), and patients unlikely to benefit or having failed treatment with intravenous (IV) recombinant tissue plasminogen activator (rtPA), there is a need for alternative methods of revascularization which can improve outcomes without increasing the risk for intracranial hemorrhage. The uses of various neurothrombectomy devices (clot retrievers, aspiration/suction devices, snare-like devices, ultrasonography technologies, and lasers) have been examined in these populations. Currently, two neurothrombectomy devices are FDA-cleared through the FDA 510(k) process: the MERCI clot retriever and the Penumbra System. Various ongoing clinical trials are currently evaluating the impact of these devices, as well as other (off-label) neurothrombectomy devices, for the treatment of acute ischemic stroke. The goal of this technical brief is to describe neurothrombectomy devices currently being used or actively investigated in the treatment of patients with acute ischemic stroke and to summarize the evidence supporting their use.

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Technical Briefs are designed to provide an overview of key issues related to clinical intervention or health care services, especially those for which there are limited published data or protocol-driven studies. They provide an early objective description of the state of science, a potential framework for assessing applications and implications, a summary of ongoing research, and information on future research needs.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov/reports/final.cfm.

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Effective Health Care

Methods

We developed a list of neurothrombectomy devices based on the FDA Center for Device and Radiological Health (CDRH) guidance definition of a neurothrombectomy device, published literature, and a search of the FDA CDRH's database to identify neurothrombectomy devices that have received FDA clearance (510(k) documents).

Systematic literature searches were conducted of MEDLINE, the Cochrane Central Register of Controlled Trials, SCOPUS, Web of Science, and the Cochrane Database of Systematic Reviews, from the earliest possible date through November 2010. Grey literature searches were also conducted, utilizing Google, clinicaltrials.gov, and manual searching techniques.

Two investigators independently screened citations at the abstract level to identify potentially relevant studies, case series, and case reports. Throughout this technical brief, our use of the terminology "studies" will refer only to prospective, single-arm studies or retrospective studies enrolling consecutive patients. The terminology "reports" will refer to the latter studies in addition to case series and case reports. Potentially eligible citations were retrieved for full-text review. We included human studies of any design, case series, and case reports as long as they included patients with an acute ischemic stroke and reported at least one outcome of interest. We included only reports in English in our qualitative review of the literature.

Two investigators independently abstracted data from eligible reports, and disagreements were resolved by a third investigator. We obtained the following information from each report: author identification, year of publication, study design characteristics, study population, patient baseline characteristics, disease severity, location of occluded artery, time from symptom onset to device deployment or angiography, use of concurrent standard medical therapies, whether outcomes assessment was blinded, and the device used. Effectiveness outcomes included: recanalization as measured by post-Thrombolysis in Myocardial Infarction (TIMI) flow grade or similar methodology, mortality, modified Rankin Scale (mRS), National Institutes of Health Stroke Scale (NIHSS) score, Barthel Index, and Glasgow Outcome Scale (GOS). Harms included failure to deploy the device or remove the clot, device breakage or fracture, perforation, dissection, thrombus formation, vasospasm, or hemorrhage.

We used descriptive statistics and summative tables to synthesize data regarding study designs, clinical and treatment characteristics, effectiveness outcomes, and adverse events reported. We created study density figures to summarize the totality of information available on the effectiveness and safety of these devices.

Results

Key Question 1. What are the different types of neurothrombectomy devices in use or in development for treatment of acute ischemic stroke?

Table A provides a list of the various neuthrombectomy classes (clot retrievers, aspiration/suction devices, snare-like devices, ultrasonography technologies, and lasers) and devices in those classes.

Neurothrombectomy devices: (1) allow patients to avoid or reduce the use of pharmacologic thrombolysis, thereby minimizing the risk for intracerebral hemorrhage (ICH); (2) can be used beyond the short timeframe to which rtPA is limited; (3) may provide more rapid recanalization than thrombolytics; and (4) can provide a treatment option for thrombi more resistant to fibrinolytic breakdown. However, the technical difficulty of navigating mechanical devices into the intracranial circulation may result in direct trauma to the neurovasculature (including vasospasm, vessel dissection, perforation, or rupture), and fragmenting thrombi may subsequently embolize into previously unaffected vessels and cerebral territories. In addition, the procedure itself carries risks, including the need for intubation and heavy sedation, which have been associated with worse outcomes.

Only the MERCI clot retriever and the Penumbra System are FDA cleared for use in patients with an acute ischemic stroke to restore perfusion. Other devices have FDA indications ranging from retrieval of intravascular foreign bodies to infusion of fluids into the peripheral vasculature. Data on the utilization of these various devices are limited.

Recent and ongoing studies are evaluating the use of "retrievable" intracranial stents that are meant to provide immediate recanalization and then be removed along with clot trapped within the stent matrix. A recent prospective, single-center pilot study reported on the safety and efficacy of a retrievable stent in 20 acute stroke patients with a large vessel occlusion who were either refractory to or ineligible for IV rtPA therapy. The stents were deployed for from 1 to 2 minutes before retrieval, with 18 of 20 (90 percent) of patients achieving successful revascularization. Six patients (30 percent) had asymptomatic ICH while 2 patients (10 percent) experienced symptomatic ICH.

Table A. Neurothrombectomy devices in use

Device Class	Company Name	FDA Indication	In Clinical Use?
Aspiration/Suction			
Amplatz Thrombectomy	Ev3 Medical	Mechanical dissolution of thrombus within dialysis fistulae	No longer marketed
AngioJet	Possis	Breaking apart or removing of thrombus in peripheral veins or arterio-venous access conduits	Yes
NeuroJet	Possis	N/A	No longer marketed
Oasis Thrombectomy	Boston Scientific	Removing thrombus from hemodialysis access grafts	No longer marketed
Penumbra	Penumbra, Inc.	Revascularization of patients with acute ischemic stroke	Yes
Vasco +35	Balt Extrusion	N/A	Not in U.S.
Clot Retriever			
Attractor-18	Boston Scientific	N/A	No longer marketed
Catch	Balt Extrusion	N/A	Not in U.S.
In-Time	Boston Scientific	Retrieval of intravascular foreign objects in peripheral vascular, neurovasculature, and cardiovasculature	No longer marketed
MERCI	Concentric Medical	Restore blood flow in the neurovasculature	Yes
Phenox	Phenox GmbH	N/A	Not in U.S.
TriSpan	Boston Scientific	N/A	No longer marketed

Table A. Neurothrombectomy devices in use (continued)			
Device Class	**Company Name**	**FDA Indication**	**In Clinical Use?**
Ultrasonography			
EKOS	EKOS Corporation	Infusion of fluids into peripheral vasculature	Yes
OmniWave	OmniSonics	Removal of thrombus and infusion of fluids into peripheral vasculature	No longer marketed
Snare			
Alligator	Chestnut Medical Technologies, Inc.	Peripheral and neurovasculature foreign body removal	Yes
Amplatz Gooseneck	Ev3 Medical	Retrieval and manipulation of atraumatic foreign bodies in coronary and peripheral cardiovascular system and the extra-cranial neurovascular anatomy	Yes
EnSnare Device	Merit Medical Systems, Inc.	Retrieval and manipulation of foreign objects in the cardiovascular system or hollow viscous	Yes
Neuronet	Boston Scientific	N/A	No longer marketed
Soutenir	Solution	N/A	Not in U.S.
Laser			
EPAR	Endovasix Inc.	N/A	No longer marketed
LaTIS	Spectranetics	Removal of thrombus from vascular grafts	No longer marketed

EPAR=Endovascular Photoacoustic Recanalization; FDA=Food and Drug Administration; N/A=not applicable; U.S.=United States.

Key Question 2. From a systematic scan of studies of different types of neurothrombectomy devices, what are the type(s) of devices, study designs and sizes, patient characteristics, comparators used in comparative studies, lengths of followup, concurrent or prior therapies, outcomes measured, and adverse events, harms, and safety issues reported?

A total of 2,054 citations were identified, 378 of which were retrieved for full-text review. A total of 87 articles were ultimately included in the study. Sixty-two articles (71 percent) were case series or case reports, 18 (21 percent) were prospective single-arm studies, and 7 (8 percent) were non-comparative, retrospective studies enrolling consecutive patients. These studies were published in full-text (74 percent) or abstract form (26 percent). Fifteen of 25 studies (60 percent) were published between 2008 and 2010. Only 3 of 18 (17 percent) prospective and 1 of 7 retrospective studies clearly stated that they utilized blinded outcome assessment.

The largest percentage of overall reports (40 percent) and prospective studies (31 percent) were for the MERCI clot retriever. The Penumbra System had 10 reports, of which 4 were prospective. For off-label

devices, two studies were conducted with EKOS, and one each with Phenox, Amplatz Gooseneck, AngioJet, EPAR, Neuronet, and LaTIS.

The size of prospective single-arm studies ranged from 2 to 164 patients, and retrospective studies ranged from 15 to 114 patients. The largest studies evaluated the MERCI clot retriever (numbers ranged from 18 to 164 patients) and the Penumbra System (numbers ranged from 15 to 125 patients). Studies of "off-label" devices ranged from 2 to 45 patients.

The remaining 62 of 87 (71 percent) articles were either case series or case reports. In total, 191 patients were evaluated with a neurothrombectomy device in case series and case reports. The combined number of patients evaluated in a case series or case report with a neurothrombectomy device ranged from 0 (EPAR and LaTIS lasers) to 75 (MERCI clot retriever). Case series and reports provide the majority of data on off-label use (n=109 patients) of potential neurothrombectomy devices to treat acute ischemic stroke.

Studies typically enrolled patients older than 18 years of age, with baseline NIHSS scores ≥8 (or ≥10), presenting within 8 hours of stroke symptom onset (or up to 24 hours for EKOS, EPAR, or LaTIS if a posterior circulation occlusion was identified), and having a complete or near complete (TIMI 0-1) occlusion of a treatable large intracranial vessel. Common exclusion criteria included advanced age, large brain infarction, abnormal hemostasis, severe or uncontrolled hypertension, hypoglycemia, and pregnancy. Studies also enrolled patients with contraindications to receive IV rtPA due to risks of adverse events, reporting outside a 3-hour window from symptom onset to IV rtPA, or who failed (target vessel not recanalized as determined by immediate angiography following the procedure) IV rtPA treatment. The one exception was the EKOS study by Tomsick in 2008. The EKOS device is designed to infuse intra-arterial (IA) thrombolytic therapy, and in this study EKOS was used along with reduced-dose IV rtPA within the first 3 hours of stroke symptoms.

The mean/median baseline NIHSS range was 15 to 25 across studies. The range for mean/median age was 42 to 68 years and studies enrolled 20 to 57 percent females. In studies where data were provided, the majority of patients had pre-device TIMI 0 or 1 flow.

Mean/median time from stroke symptom to either angiography or device deployment ranged from 141 to 388 minutes, well within the 8-hour timeframe suggested by the FDA CDRH guidance. The primary embolus was most commonly in an anterior vessel (14 studies enrolled >60 percent anterior occlusion patients). However, some studies focused heavily on posterior occlusions. Only 1 of 25 studies (4 percent) reported including patients with occlusions in other areas and 6 studies were unclear about the location of occlusion.

A majority of case series and case reports included patients who would typically meet prospective study inclusion criteria. However, some case series and reports included both pediatric patients, those older than 80 years of age, and those with a baseline NIHSS score below or above the typical enrollment threshold of 8 to 10. Finally, some case series and reports for the Penumbra System, MERCI clot retriever, TriSpan clot retriever, In-Time clot retriever, and Neuronet and Amplatz Gooseneck snares, enrolled patients with symptom-to-angiography or device deployment times outside the 8-hour window used in prospective and retrospective studies of these devices. The location of emboli reported in case series and case reports was predominantly anterior (72 percent) and posterior circulation (24 percent).

No direct human comparative studies were identified during our scan of the neurothrombectomy literature. All prospective and retrospective studies reported recanalization success after neurothrombectomy device deployment. The longest durations of followup in the majority of prospective and retrospective studies reporting effectiveness outcomes were either 30 days or 90 days post-procedure. The timing of NIHSS evaluation was more variable with the longest duration of followup ranging from 24-hours to 90-days post-procedure. Safety endpoints were typically monitored over shorter lengths of time, such as the first 24 hours or until discharge. The reporting of followup outcomes in case series and case reports was variable. Of the 71 total device reports, nearly half did not report data on effectiveness or safety outcomes after patient discharge. In those reports that did, length of followup ranged from 6 weeks to 24 months; the most commonly reported length of followup was 90 days.

Prospective and retrospective neurothrombectomy studies focus on patients contraindicated to receive IV rtPA, reporting outside the recommended 3-hour window, or refractory to or failing IV rtPA treatment. Consequently, the use of IV rtPA among studies ranged from 0 to 100 percent. The one exception was the aforementioned EKOS study. Concurrent or rescue therapies in identified studies, case series, and reports included intra-arterial thrombolytics, cerebral artery angioplasty, and stenting.

Table B summarizes all identified reports (prospective and retrospective studies, case series, and reports) of neurothrombectomy devices by device classification and the effectiveness endpoints evaluated.

Table B. Effectiveness evidence for neurothrombectomy devices (n=1,311)
(Reported as prospective/retrospective/case series or reports)

			Devices														
			Clot Retriever (n=847)			Aspiration/ Suction (n=411)			Snare (n=94)			Ultrasound Technology (n=50)			Laser (n=36)		
			P	R	C	P	R	C	P	R	C	P	R	C	P	R	C
Reported Outcomes	Recanalization	Studies	7	4	34	5	3	10	2	0	24	1	0	1	2	0	0
		Patients	524	220	98	211	173	24	14	0	74	29	0	7	36	0	0
	mRS	Studies	5	1	11	5	3	4	2	0	9	1	0	1	1	0	0
		Patients	440	18	11	213	173	16	12	0	33	14	0	1	34	0	0
	Death#	Studies	5	1	16	5	3	7	2	0	9	1	0	0	1	0	0
		Patients	450	18	38	184	173	23	2	0	53	14	0	0	34	0	0
	NIHSS	Studies	3	0	15	4	3	5	2	0	11	1	0	0	1	0	0
		Patients	371	0	31	211	173	12	12	0	53	14	0	0	34	0	0
	BI	Studies							1	0	0	1	0	0			
		Patients							5	0	0	14	0	0			
	GOS	Studies										1	0	0			
		Patients										14	0	0			

Darker shading represents more frequent evaluation or larger number of patients evaluated.

BI=Barthel Index; C=case report/case series; GOS=Glasgow Outcome Scale; mRS=modified Rankin Scale; n=the total number of patients evaluated for any effectiveness or safety endpoint; NIHSS=National Institutes of Health Stroke Scale; P=prospective; R=retrospective.

#Death included if patients were followed up for any duration of time after hospital discharge.

All prospective or retrospective studies reported recanalization results. The NIHSS score was reported in 13 of 25 (52 percent) identified studies and mRS≤2 was reported in 17 of 25 (68 percent) studies. NIHSS, mRS≤2, and mortality endpoints were reported in 20 percent, 50 percent, and 50 percent of MERCI clot retriever; 100 percent, 100 percent, and 100 percent of Penumbra System; and 50 percent, 63 percent, and 63 percent of off-label device studies.

Table C summarizes all identified reports of neurothrombectomy devices by device classification and the safety endpoint(s) evaluated.

Other adverse events evaluated in the neurothrombectomy literature included perforation/dissection, other types of hemorrhage (not intracerebral), thrombus formation (proximal, adjacent, or distal to the clot site), failure to deploy the device, device breakage/fracture, and vasospasm. During prospective or retrospective studies, the proportion of patients per study experiencing an instance of symptomatic or asymptomatic ICH, other bleeding, perforation or dissection, or thrombus formation were reported in 50 percent, 50 percent, 30 percent, 40 percent, and 20 percent of MERCI clot retriever, respectively; 100 percent, 71 percent, 29 percent, 43 percent, and 43 percent of Penumbra System; and 63 percent, 38 percent, 0 percent, 63 percent, and 38 percent of off-label device studies, respectively. Device failure-to-deploy, device fracture or breakage, and vasospasm data were infrequently reported in studies.

Key Question 3: What are the variables associated with use of the devices that may impact outcomes (e.g. time to deployment, training/expertise of interventionalist, location of infarct, concurrent therapies)?

The effects of predictor variables on select outcomes identified by researchers during neurothrombectomy studies are summarized in Table D.

Table C. Safety endpoint evidence for neurothrombectomy devices (n=1,311)
(Reported as prospective/retrospective/case series or reports)

			Devices														
			Clot Retriever (n=847)			Aspiration/ Suction (n=411)			Snare (n=94)			Ultrasound Technology (n=50)			Laser (n=36)		
			P	R	C	P	R	C	P	R	C	P	R	C	P	R	C
Reported Adverse Events	SICH	Studies	5	0	8	5	3	3	1	0	10	2	0	0	1	0	0
		Patients	382	0	39	213	173	10	7	0	37	49	0	0	34	0	0
	AICH	Studies	5	0	8	5	2	3	1	0	10				1	0	0
		Patients	382	0	39	213	158	10	7	0	37				34	0	
	Perforation/ Dissection	Studies	3	0	2	3	1	2	1	0	4	2	0	0	1	0	0
		Patients	190	0	17	157	15	14	7	0	21	49	0	0	34	0	0
	Thrombus Formation	Studies	2	0	5	3	1	1	2	0	3						
		Patients	165	0	20	157	15	4	12	0	9						
	Other Hemorrhage	Studies	2	0	4	1	1	0	0	0	3						
		Patients	166	0	25	20	15	0	0	0	13						

Darker shading represents more frequent evaluation or larger number of patients evaluated.

AICH=asymptomatic intracerebral hemorrhage; C=case report/case series; n=the total number of patients evaluated for any effectiveness or safety endpoint; P=prospective; R=retrospective; SICH=symptomatic intracerebral hemorrhage.

Table D. Effect of various variables on post-neurothrombectomy device outcomes

	Clinical Outcomes				
Predictor Variables	**Recanalization**	**NIHSS Improvement**	**Hemorrhage***	**mRS≤2**	**Death**
Recanalization∞	–	B	–	B	B
Older Age	–	–	–	H	H
Higher SBP	–	H	–	H	H
Higher Baseline NIHSS	I	–	–	H	H
ICA Occlusion Site (vs. mostly MCA)	I	–	–	I	H
Abnormal Hemostasis#	I	–	I	H	I
Prior IV rtPA	I	–	I	I	I
Concomitant IA thrombolytics	B	–	I	I	I
Prior Stroke	–	–	–	–	H
Longer Procedure Duration	–	–	–	H	I
Right Brain Infarct	–	–	–	H	–

B=beneficial; H=harmful; I=indeterminate (no statistically significant effect); IA=intra-arterial; ICA=internal carotid artery; IV rtPA=intravenous recombinant tissue plasminogen activator; MCA=middle cerebral artery; mRS=modified Rankin Scale; NIHSS=National Institutes of Health Stroke Scale; SBP=systolic blood pressure.

*including symptomatic and asymptomatic hemorrhage.

#INR>1.7, PTT>45 and/or platelet count <100,000.

∞Revascularization as defined by achieving TIMI 2-3 flow at the site of primary occlusion.

Evaluated predictors of outcome (Table D) in these patients treated with a neurothrombectomy device include demographic, co-morbid disease, stroke severity, and stroke treatment variables. These predictors were evaluated in studies (or pooled analyses) of the MERCI clot retriever and the Penumbra System. Of particular note, recanalization was the only variable that was found to be predictive of clinical benefit (achieving a mRS≤2) as well as lower mortality. These results are similar to those found in an earlier meta-analysis as well as a pooled analysis of the IMS I and II trials, where reduced-dose IV followed by IA thrombolysis was associated with good outcomes. In addition to these variables, researchers have suggested that the presence of collateral circulation, lesion volume, and cerebral perfusion pressure have also been linked to outcomes in acute ischemic stroke patients.

In a meta-analysis by Stead and colleagues evaluating neurothrombectomy devices, younger age and lower NIHSS score at presentation had beneficial effects on achieving a mRS≤2 (p=0.001). Patients with posterior circulation occlusions were found to have higher odds of 90-day mortality compared to those with anterior occlusions (either internal carotid or middle cerebral arteries).

No studies provided data assessing the relationship between the training of interventionalists and outcomes in patients treated with neurothrombectomy devices. However, studies of emerging technologies over the past 20 years have suggested that inadequate physician training and experience can adversely affect clinical outcomes. Of note, upon qualitative review, the proportion of patients recanalized in retrospective

(real-world) studies did not appear to be lower than that of the prospective, single-arm studies, for either MERCI or Penumbra System studies. This suggests that practicing clinicians may be achieving outcomes similar to those clinicians involved with clinical trials, which would indicate that practicing clinicians are receiving adequate training.

Two reports have been written and approved by multiple neuroscience societies detailing the minimum training requirements for those performing neuroendovascular procedures (including neurothrombectomy devices) in patients with acute ischemic stroke, and setting out performance standards that should be adopted to assess outcomes.

Discussion

Neurothrombectomy devices are a treatment option in patients with an acute ischemic stroke. The specific population most likely to benefit from these devices is still under investigation. Current studies have involved patients with large vessel occlusions, high baseline NIHSS scores, and those either unlikely to respond or who have failed IV rtPA therapy. Only two neurothrombectomy devices, the MERCI clot retriever and the Penumbra System, are cleared by FDA to restore perfusion in patients with acute ischemic stroke. A majority of available data relates to the two cleared devices.

We did not identify any direct human comparative studies of neurothrombectomy devices to IV rtPA or each other. Instead, investigators frequently studied devices as part of prospective single-arm studies, non-comparative retrospective studies enrolling consecutive patients, or case series or case reports. In this technical brief, our main objective was limited to describing neurothrombectomy devices currently being used or actively investigated in the treatment of patients with acute ischemic stroke and summarizing the evidence supporting their use. We did not draw conclusions regarding their effectiveness or safety.

A previous systematic review of neurothrombectomy devices by Stead and colleagues was identified during our literature scan. The literature search on which their review was based extended only through March 2006 and consequently did not include the majority of the highest quality data on neurothrombectomy devices (including that of the MERCI and Penumbra Systems). Thus, our technical brief should represent the most up-to-date review of the literature at this time. Unlike our review, Stead and colleagues quantitatively compared pooled device results to a control group derived from their own institution's stroke population. They found that when compared with a similar matched cohort, the neurothrombectomy patients had good functional recovery (mRS≤2) in 34.5 percent of patients compared with 10.7 percent of patients matched for age, sex, and NIHSS score, suggesting that the neurothrombectomy group was nearly 15 times more likely than the control group to have good functional recovery. While perhaps the best "controlled" data available to date, this analysis is fraught with limitations, including the fact that the neurothrombectomy cohort was not homogeneous, the comparison was to a single-center historically concurrent cohort, and individuals were not randomly allocated.

Eleven ongoing studies are evaluating at least one neurothrombectomy device in acute ischemic stroke listed on the http://www.clinicaltrials.gov/ Web site or mentioned in previous review articles. The first of these eleven studies is estimated to end sometime in 2010. All studies appear to be enrolling patients based upon inclusion and exclusion criteria that are similar to those already used by the prospective and retrospective studies detailed throughout this report. One exception is the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) trial, which will allow patients to receive IV rtPA up to 4.5 hours after symptom onset. Seven of these studies have randomized, controlled designs with projected enrollment ranging from 20 to 900. The other four studies have prospective, observational designs ranging from 200 to 2000 projected participants. Six of the seven randomized controlled trials are allowing the use of multiple neurothrombectomy devices; most compare the use of neurothrombectomy devices to best medical therapy (with or without IV rtPA). Both the MERCI clot retriever and the Penumbra System have prospective observational studies in progress. Compared to previous, similarly designed studies of these agents, these studies will enroll much larger sample sizes (n=2,000 and 3,000, respectively).

The use of advanced imaging techniques should be incorporated into future randomized controlled trials to aid in identifying those patients most likely to benefit from neurothrombectomy devices. In addition, for those patients with contraindications or who are refractory to IV rtPA, it is unclear which device is the most efficacious or safe. It would seem reasonable to conduct studies to answer such research gaps using a randomized controlled trial design, powered to show equivalency or non-inferiority of devices. These studies should also evaluate the impact on health-related quality of life of neurothrombectomy devices.

Summary

Currently available neurothrombectomy devices offer intriguing treatment options in patients with acute ischemic stroke, although a paucity of high quality research currently exists. There remains a need for further research on the topic, including randomized controlled trials to determine the optimal device(s) to use, and the patient populations most likely to benefit from their use. Additionally, studies of neurothrombectomy devices against contemporaneous controls investigating whether these devices truly treat final health outcomes associated with stroke rather than improving recanalization alone are warranted. Results of ongoing studies will likely only begin to address some of these questions.

Full Report

This executive summary is part of the following document: Baker WL, Colby JA, Tongbram V, Talati RA, Silverman IE, White CM, Kluger J, Coleman CI. Neurothrombectomy Devices for Treatment of Acute Ischemic Stroke. Technical Brief No. 4 (Prepared by University of Connecticut/Hartford Hospital Evidence-based Practice Center under Contract No. 290-2007-10067-I.) Rockville, MD: Agency for Healthcare Research and Quality. January 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm

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January 2011

Review

Acute Stroke Intervention
A Systematic Review

Shyam Prabhakaran, MD, MS; Ilana Ruff, MD; Richard A. Bernstein, MD, PhD

IMPORTANCE Acute ischemic stroke is a major cause of mortality and morbidity in the United States. We review the latest data and evidence supporting catheter-directed treatment for proximal artery occlusion as an adjunct to intravenous thrombolysis in patients with acute stroke.

OBJECTIVE To review the pathophysiology of acute brain ischemia and infarction and the evidence supporting various stroke reperfusion treatments.

EVIDENCE REVIEW Systematic literature search of MEDLINE databases published between January 1, 1990, and February 11, 2015, was performed to identify studies addressing the role of thrombolysis and mechanical thrombectomy in acute stroke management. Studies included randomized clinical trials, observational studies, guideline statements, and review articles. Sixty-eight articles (N = 108 082 patients) were selected for review.

FINDINGS Intravenous thrombolysis is the mainstay of acute ischemic stroke management for any patient with disabling deficits presenting within 4.5 hours from symptom onset. Randomized trials have demonstrated that more patients return to having good function (defined by being independent and having slight disability or less) when treated within 4.5 hours after symptom onset with intravenous recombinant tissue plasminogen activator (IV rtPA) therapy. Mechanical thrombectomy in select patients with acute ischemic stroke and proximal artery occlusions has demonstrated substantial rates of partial or complete arterial recanalization and improved outcomes compared with IV rtPA or best medical treatment alone in multiple randomized clinical trials. Regardless of mode of reperfusion, earlier reperfusion is associated with better clinical outcomes.

CONCLUSIONS AND RELEVANCE Intravenous rtPA remains the standard of care for patients with moderate to severe neurological deficits who present within 4.5 hours of symptom onset. Outcomes for some patients with acute ischemic stroke and moderate to severe neurological deficits due to proximal artery occlusion are improved with endovascular reperfusion therapy. Efforts to hasten reperfusion therapy, regardless of the mode, should be undertaken within organized stroke systems of care.

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Stroke is a leading cause of disability in the United States and the fifth leading cause of death.[1] An acute ischemic stroke (AIS) occurs when an artery supplying the brain becomes occluded, leading to the death of brain tissue and focal neurological deficits. An estimated 700 000 ischemic strokes occur in the United States each year, costing more than $70 billion to society.[1] The toll exerted on individual patients and families by a devastating stroke is incalculable; most elderly patients fear a disabling stroke more than they fear death.[2] Thus, improving neurological outcome after an ischemic stroke is a major societal priority and has attracted intense attention of clinical and basic researchers, government funding agencies, and industry. Consistent with animal models of ischemia, the overarching goal of AIS therapy is relieving the arterial occlusion (recanalization) and restoring cerebral blood flow (reperfusion) as soon as possible to reduce tissue injury and improve outcomes.

There is general consensus based on strong evidence that in patients presenting within 4.5 hours of symptom onset, intravenous recombinant tissue plasminogen activator (IV rtPA) therapy is beneficial. However, many patients present with occlusion of a large proximal artery beyond 4.5 hours or have contraindications to systemic thrombolysis (ie, recent major surgery or active bleeding). For these reasons and because proximal artery occlusions are relatively resistant to intravenous thrombolysis, catheter-based or intra-arterial approaches to directly remove the clot and restore blood flow to the brain have been the focus of recent randomized clinical trials. We review acute stroke treatment with an emphasis on intra-

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Thrombolysis (different doses, routes of administration and agents) for acute ischaemic stroke (Review)

Wardlaw JM, Koumellis P, Liu M



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[Intervention Review]

Thrombolysis (different doses, routes of administration and agents) for acute ischaemic stroke

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ABSTRACT

Background

Stroke is a leading cause of death and disability world wide. Thrombolysis with recombinant tissue plasminogen activator (rt-PA) is licensed for treatment of acute ischaemic stroke in the early hours after symptom onset. It has been shown in randomised controlled trials (RCTs) and the 2009 Cochrane review of thrombolysis for acute ischaemic stroke to reduce dependency but at the increased risk of intracranial haemorrhage. Methods to reduce the risk of haemorrhage while retaining or enhancing the benefit could increase the use of thrombolytic treatment. While most available information comes from RCTs of intravenous rt-PA at 0.9 mg/kg, it is possible that other doses, drugs and other routes of administration might increase benefit and reduce the hazard.

Objectives

To assess the risks and benefits of different thrombolytic agents, doses and routes of administration for the treatment of acute ischaemic stroke.

Search methods

We searched the Cochrane Stroke Group Trials Register (May 2012), MEDLINE (1966 to May 2012) and EMBASE (1980 to May 2012). We handsearched journals and conference proceedings, searched ongoing trials registers and contacted pharmaceutical companies and researchers.

Selection criteria

Unconfounded randomised and quasi-randomised trials of different doses of a thrombolytic agent, or different agents, or the same agent given by different routes, in people with confirmed acute ischaemic stroke.

Data collection and analysis

Two review authors independently assessed trial eligibility and quality, and extracted the data using a structured proforma. We cross-checked and resolved discrepancies by discussion to reach consensus. We obtained translations and additional information from study authors where required.

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Endovascular Intracranial Administration of Non-Thrombolytics

CPT code:

61650 Endovascular intracranial prolonged administration of pharmacologic agent(s) other than for thrombolysis, arterial, including catheter placement diagnostic angiography, and imaging guidance, initial vascular territory
61651 Each additional vascular territory

Issue: Various agents can be administered in the brain vasculature. However, the main use of these codes appears to be in the administration of vasodilators to treat cerebral vasospasm after intracranial hemorrhage. There are experimental reports of the use of sclerotherapeutic agents for the treatment of cerebral aneurysms; however, clipping or using intravascular coils remains the standard method for closing aneurysms. This CPT code may be used for infusion of chemotherapeutic agents for CNS cancers.

Because the main utility of these codes appears to be for the administration of vasodilators, the evidence review below is limited to this indication. The major treatment of cerebral vasospasm appears to be administration of medications via peripheral or central IV.

Similar codes: 61640-61642 (Balloon dilatation of intracranial vasospasm, percutaneous) appear on line 200 SUBARACHNOID AND INTRACEREBRAL HEMORRHAGE/HEMATOMA; CEREBRAL ANEURYSM; COMPRESSION OF BRAIN Treatment: BURR HOLES, CRANIECTOMY/CRANIOTOMY

Previous code: 37202 (Transcatheter therapy, infusion other than for thrombolysis, any type (eg Spasmolytic, vasoconstrictive) was previously used for this procedure. 37202 has been deleted for 2016. 37202 was previously on lines 83 PHLEBITIS AND THROMBOPHLEBITIS, DEEP, 239 LIMB THREATENING VASCULAR DISEASE, INFECTIONS, AND VASCULAR COMPLICATIONS, 257 ARTERIAL EMBOLISM/THROMBOSIS: ABDOMINAL AORTA, THORACIC AORTA, 285 BUDD-CHIARI SYNDROME, AND OTHER VENOUS EMBOLISM AND THROMBOSIS, **299 CANCER OF BRAIN AND NERVOUS SYSTEM**, 352 NON-LIMB THREATENING PERIPHERAL VASCULAR DISEASE, and **419 TRANSIENT CEREBRAL ISCHEMIA; OCCLUSION/STENOSIS OF PRECEREBRAL ARTERIES WITHOUT OCCLUSION**.

Evidence

1) **Kimball 2011**, review of endovascular management of cerebral vasospasm
    a. N=49 articles
    b. Most of the available studies investigated intra-arterial papaverine or balloon angioplasty. Both have generally been shown to successfully treat vasospasm and improve neurological condition, with no clear benefit from one treatment compared with another. There are reports of complications with both therapies including vessel rupture during angioplasty, intracranial hypertension, and possible neurotoxicity associated with papaverine. Limited data are available evaluating nicardipine or verapamil, with positive benefits reported with nicardipine and inconsistent benefits with verapamil.

Expert guidelines

1) **Conolly 2012**, AHA/ASA guidelines for management of subarachnoid hemorrhage (PDF is not included due to length)
    a. Oral nimodipine should be administered to all patients with aSAH *(Class I; Level of Evidence A*
    b. Maintenance of euvolemia and normal circulating blood volume is recommended to prevent DCI *(Class I; Level of Evidence B).*
    c. Prophylactic hypervolemia or balloon angioplasty before the development of angiographic spasm is not recommended *(Class III; Level of Evidence B).*
    d. Induction of hypertension is recommended for patients with DCI unless blood pressure is elevated at baseline or cardiac status precludes it *(Class I; Level of Evidence B).*
    e. Cerebral angioplasty and/or selective intra-arterial vasodilator therapy is reasonable in patients with symptomatic cerebral vasospasm, particularly those who are not rapidly responding to hypertensive therapy *(Class IIa; Level of Evidence B*).
2) **Deringer 2011**, Neurocritical Care Society consensus statement (PDF not included due to length)
    a. There was wide international variation in the use of endovascular therapies with some groups strongly recommending their use and other not utilizing them at all
    b. Recommendation: Endovascular treatment using intra-arterial vasodilators and/or angioplasty may be considered for vasospasm related DCI (moderate quality evidence-strong recommendation).
    c. Recommendation: The timing and triggers of endovascular treatment of vasospasm remains unclear, but generally rescue therapy for ischemic symptoms that remain refractory to medical treatment should be considered. The exact timing is a complex decision which should consider the aggressiveness of the hemodynamic intervention, the patients' ability to tolerate it, prior evidence of large artery narrowing, and the availability of and the willingness to perform angioplasty or infusion of intra-arterial agents (moderate quality evidence—strong recommendation).
3) **Steiner 2013**, European Stroke Organization guideline of treatment of subarachnoid hemorrhage (PDF not included due to length)
    a. no recommendations for angioplasty or intra-arterial vasodilators

Summary:

Little evidence was found to support the use of balloon angioplasty (currently on covered line) or intra-arterial vasodilators (current code under review), but both procedures are recommended as possible therapies by expert guidelines which rate the underlying evidence to be of moderate strength. These procedures appear to be rarely done and not widely studied.

HERC staff recommendations:

1) Add **61650-61651** (Endovascular intracranial prolonged administration of pharmacologic agent(s) other than for thrombolysis, arterial, including catheter placement diagnostic angiography, and imaging guidance) to the lines shown below
    a. **299** CANCER OF BRAIN AND NERVOUS SYSTEM
        i. Consistent with current code placement
    b. **322** STROKE
        i. Appropriate diagnoses: I67.841 (Reversible cerebrovascular vasoconstriction syndrome) and I67.848 (Other cerebrovascular vasospasm and vasoconstriction)
        ii. Add coding specification to line 322: "CPT 61650-61651 appear on this line only for pairing with ICD-10 I67.84x."
    c. **419** TRANSIENT CEREBRAL ISCHEMIA; OCCLUSION/STENOSIS OF PRECEREBRAL ARTERIES WITHOUT OCCLUSION.
        i. Consistent with current code placement
    d. Recommendations above based on expert guideline recommendations; there is little evidence available about the effectiveness of this therapy for intracranial vasospasm. Inclusion on the CNS cancer line is consistent with current code placement
2) Alternate placement: **Services Recommended for Non-Coverage Table**
    a. Difficult to determine actual therapy indicated by this code
    b. This code series can be revisited in the future in providers request it for specific applications
    c. If placed on SRNC, HERC staff will need to review 61640-61642 (Balloon dilatation of intracranial vasospasm, percutaneous) for possible removal from line 200 SUBARACHNOID AND INTRACEREBRAL HEMORRHAGE/HEMATOMA; CEREBRAL ANEURYSM; COMPRESSION OF BRAIN Treatment: BURR HOLES, CRANIECTOMY/CRANIOTOMY and placement on SRNC as well as the evidence supporting these therapies is of similar quality and strength (poor)

neurocritical care society Neurocrit Care (2011) 15:336–341
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REVIEW

Critical Care Guidelines on the Endovascular Management of Cerebral Vasospasm

Matthew M. Kimball · Gregory J. Velat · Brian L. Hoh · The Participants in the International Multi-disciplinary Consensus Conference on the Critical Care Management of Subarachnoid Hemorrhage

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Abstract Cerebral vasospasm and delayed cerebral ischemia account for significant morbidity and mortality after aneurysmal subarachnoid hemorrhage. While most patients are managed with triple-H therapy, endovascular treatments have been used when triple-H treatment cannot be used or is ineffective. An electronic literature search was conducted to identify English language articles published through October 2010 that addressed endovascular management of vasospasm. A total of 49 articles were identified, addressing endovascular treatment timing, intra-arterial treatments, and balloon angioplasty. Most of the available studies investigated intra-arterial papaverine or balloon angioplasty. Both have generally been shown to successfully treat vasospasm and improve neurological condition, with no clear benefit from one treatment compared with another. There are reports of complications with both therapies including vessel rupture during angioplasty, intracranial hypertension, and possible neurotoxicity associated with papaverine. Limited data are available evaluating nicardipine or verapamil, with positive benefits reported with nicardipine and inconsistent benefits with verapamil.

The Participants in the International Multi-disciplinary Consensus Conference: Michael N. Diringer, Thomas P. Bleck, Nicolas Bruder, E. Sander Connolly Jr, Giuseppe Citerio, Daryl Gress, Daniel Hanggi, J. Claude Hemphill III MAS, Brian Hoh, Giuseppe Lanzino, Peter Le Roux, David Menon, Alejandro Rabinstein, Erich Schmutzhard, Lori Shutter, Nino Stocchetti, Jose Suarez, Miriam Treggiari, MY Tseng, Mervyn Vergouwen, Paul Vespa, Stephan Wolf, Gregory J. Zipfel.

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Keywords Balloon angioplasty · Intra-arterial · Nicardipine · Papaverine · Verapamil

Introduction

Cerebral vasospasm and delayed cerebral ischemia (DCI) account for the majority of morbidity and mortality for patients who survive to undergo treatment following aneurysmal subarachnoid hemorrhage (SAH). Angiographic vasospasm is observed in 30–70% of patients between days 5 and 14 following the initial aneurysmal bleed [1, 2]. Approximately 50% of patients with angiographic vasospasm will develop DCI, with 15–20% of these patients suffering stroke or death despite maximal therapy [3, 4].

Medical management of vasospasm primarily consists of hemodynamic augmentation that is associated with significant risks of complications, such as heart failure and pulmonary edema [5]. Endovascular therapies, such as intra-arterial vasodilator administration or transluminal balloon angioplasty, might benefit patients with cerebral vasospasm when hemodynamic therapy has failed or when there is concern for complications of hemodynamic therapy.

Despite the potential benefit from endovascular therapy, clear guidelines directing use of these treatments for vasospasm after SAH are not available. The decision of when to intervene endovascularly is not clear and certain across all patients. A review of the medical literature was conducted to determine the role of endovascular treatment in the management of cerebral vasospasm.

Methods

A search was performed of the English language literature published through October 2010 using MEDLINE, the

Fetal MRI

CPT codes

74712 Magnetic resonance (eg, proton) imaging, fetal, including placental and maternal pelvic imaging when performed, first gestation
74713 each additional gestation

Issue: The new fetal MRI CPT codes were discussed at the October, 2015 VBBS meeting. There was general consensus that these codes should be placed on line 1 PREGNANCY, with a guideline. HERC staff was asked to contact maternal-fetal medicine specialists and fetal radiologists to get input into the proposed guideline.

Fetal MRI is the use of MRI technology to evaluate abnormalities, generally after the abnormality has been detected by traditional fetal ultrasound. The major use of this technology appears to be in the evaluation of CNS abnormalities, gastroschisis, and congenital diaphragmatic hernia.

Currently, fetal MRI is coded with CPT codes for pelvic MRI (CPT 72192-72197) which are diagnostic.

Expert guidelines

1) **American College of Radiology—Society for Pediatric Radiology 2015**, guideline on fetal MRI (PDF not included due to length)
    a. When an anomaly is visualized by ultrasound but the etiology remains uncertain due to the nature of the abnormality, or due to sonographic limitations from fetal lie, maternal body habitus, oligohydramnios, or small field of view, MRI can add additional information that may impact parental counseling, management, and delivery planning
    b. Multiple possible indications listed
    c. Individuals interpreting fetal MRI should be familiar with both fetal and neonatal diagnoses
    d. Prior to 18 weeks gestational age the fetal MRI study can give limited diagnostic information due to the small size of the fetus and fetal movement.
2) **Reddy 2014**, NIH/Society for Maternal-Fetal Medicine/ACOG/ACR/SPR/Society of Radiologists consensus statement on fetal MRI
    a. Targeted ultrasonography performed by an experienced sonologist must precede fetal MRI
    b. Interpretation must be done by individuals with expertise in obstetric imaging, fetal MRI, and pediatric imaging
    c. Fetal MRI is useful at further diagnosis or delineation of abnormalities in the CNS, face, neck, spine, chest, abdomen, and placenta. Fetal MRI has a useful role in assisting the planning of fetal surgery.
    d. Before 18 weeks of gestational age, fetal MRI is of limited benefit because of the small fetal size and fetal motion artifact. Magnetic resonance imaging at 20–22

weeks is a useful adjunct to ultrasonography for better evaluation and management of known or suspected anomalies. The third trimester is the optimal time for assessment of cortical development and to assess airway compromise in neck masses.

e. For the assessment of fetal anatomy, 1.5 Tesla equipment is used in conjunction with a fast T2-weighted single-shot technique.
f. Research is needed for abnormalities in cases in which MRI may add additional information beyond that available with ultrasonography, such as assessing the effect of MRI in patients with obesity where a fetal survey is inadequate; establishing a threshold for small fetal head size where MRI could provide additional information; defining the conditions in which fetal MRI can aid in assessment, such as fetal lung volumes, chest masses, spinal abnormalities, and cardiac anatomy and function; defining the incremental benefit of MRI beyond ultrasonography in cases of anhydramnios; performing additional animal and human studies for safety of fetal MRI at 1.5 Tesla, 3 Tesla, and greater Tesla; and defining the role of MRI in fetuses exposed to adverse maternal environment (eg, uteroplacental insufficiency, infection). The optimal timing of MRI as well as the appropriate functional imaging tools, such as spectroscopy and diffusion tensor imaging, need further study. A final area of research is assessment of the placenta for distinguishing between small-for-gestational-age and growth-restricted fetuses, assessment of placenta accreta, and knowledge regarding placental metabolism.

3) **Patenaude 2014**, Society of OB/Gyn Canada, practice guideline for the use of fetal MRI
    a. Fetal magnetic resonance imaging is safe at 3.0 tesla or less during the second and third trimesters. (II-2)
    b. The imaging team should consist of a technologist who fulfills the competency profile of the Canadian Association of Medical Radiation Technologists and has experience in fetal MRI, with specific training in MRI principles, sequences, and safety, and ideally a radiologist who is either trained or highly experienced in fetal MRI.
    c. Ideally, three orthogonal planes should be obtained through the fetal head and body in each sequence. The MRI protocol primarily includes T2-weighted sequences. T1-weighted, diffusion-weighted, and additional sequences may be added if indicated
    d. There are limitations in performing fetal MRI in obese patients
    e. in certain cases MRI may provide additional relevant clinical information that will facilitate perinatal counselling and management decisions
    f. Ultrasound remains the primary diagnostic tool for fetal imaging. Although MRI may provide additional relevant clinical information, fetal movement can create artifacts leading to non-diagnostic images. MRI in the obstetric patient should only be done if the ultrasound assessment is inadequate for antenatal clinical management and the desired information is required in the fetal period; on occasion it may replace neonatal MRI requiring general anaesthesia. MRI should only be performed and interpreted in centres with sufficient expertise following

a careful review of all imaging and clinical information. During the first trimester of pregnancy, MRI should be used only as a clinically necessary precaution in the case of theoretical risks.

No reviews found explicitly addressing fetal MRI at NICE, SIGN, CTAF. No policies found with Aetna, Cigna, or Blue Cross.

Expert input:

Brian Shaffer, Maternal-Fetal Medicine (MFM) at OHSU

Recommends following the ACR guideline outlined above.
(numbers refer to sections in the proposed guideline)
1)...the abnormalities should be found by an experienced Sonologist... sometimes we get referral for anomalies and the referring provider wants an MR but when we see the fetus - feel it's unnecessary.....
2)...I think the person making the decision should be experienced ---- we use MRI for very different anomalies -- from brain (most common) to complex GU - cloaca.... I believe experienced sonologist (MFM or radiologist)
3)...agree - at least 18 -- maybe 20 or 22.....
4) I think a bit more is needed here: MRI should be a 1.5 Tesla magnet and the executive summary recommends a team interpretation "Furthermore, a team approach to the interpretation of fetal MRI is essential, with involvement of the referring physician and individuals with expertise in obstetric imaging, fetal MRI, and pediatric imaging". There is an executive statement that frames this issue well (I have pasted the salient comments below).

Leo Pereira, MFM OHSU

This is well thought out and timely
I like points 1, 3, and 4
With regards to point 2 I think you need to be clear about what is meant by a fetal radiologist and how will it be documented that 2 physicians feel it's necessary? Would you require 2 names on the order?

Keith Balderson, MFM in Eugene

Recommended against having a radiologist as the gatekeeper. Recommended that the test be recommended by a MFM or not have a gatekeeper at all.
Recommended that the MRI technologist be experienced and knowledgeable, and the center be high volume.

Fetal MRI

HERC staff recommendations:

1) Add CPT 74712-74713 (fetal MRI) to line 1 PREGNANCY
2) Add the following guideline to line 1

GUIDELINE NOTE XXX, FETAL MRI

Line 1

Fetal MRI (CPT 74712-74713) is included on this line only when all of the following conditions are met:

1) Abnormalities are found on fetal ultrasound performed by an experienced sonologist which cannot be adequately further evaluated by 2D or 3D ultrasound
2) The information obtained by fetal MRI is necessary for decisions about fetal or neonatal therapy, delivery planning, or to advise a family about prognosis
3) The fetus is 18 weeks gestational age or older
4) The MRI is performed and interpreted at a center with technicians and radiologists who are either trained or highly experienced in fetal MRI and which has appropriate MRI equipment, with a minimum of a 1.5 Tesla magnet

Current Commentary

Fetal Imaging

Executive Summary of a Joint *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Society for Maternal-Fetal Medicine, American Institute of Ultrasound in Medicine, American College of Obstetricians and Gynecologists, American College of Radiology, Society for Pediatric Radiology, and Society of Radiologists in Ultrasound Fetal Imaging Workshop

*Uma M. Reddy, MD, MPH, Alfred Z. Abuhamad, MD, Deborah Levine, MD, and George R. Saade, MD, for the Fetal Imaging Workshop Invited Participants**

Given that practice variation exists in the frequency and performance of ultrasound and magnetic resonance imaging (MRI) in pregnancy, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development hosted a workshop to address indications for ultrasound and MRI in pregnancy, to discuss when and how often these studies should be performed, to consider recommendations for optimizing yield and cost effectiveness, and to identify research opportunities. This article is the executive summary of the workshop.

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**For a list of the Fetal Imaging Workshop Invited Participants, see the Appendix.*

From the Eunice Kennedy Shriver *National Institute of Child Health and Human Development, Bethesda, Maryland; Eastern Virginia Medical School, Norfolk, Virginia; Beth Israel Deaconess Medical Center, Boston, Massachusetts; and the University of Texas Medical Branch at Galveston, Galveston, Texas.*

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Since the advent of fetal ultrasonography in the 1960s, the average number of obstetric ultrasonographies per pregnancy has gradually increased. Furthermore, significant practice variation exists in the frequency and performance of ultrasonography in pregnancy. Innovations in imaging, such as magnetic resonance imaging (MRI), have added to the available tests for fetal evaluation.

To synthesize the available information regarding the role of ultrasonography and MRI in the diagnosis of fetal conditions and management of pregnancy, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Society for Maternal-Fetal Medicine, American Institute of Ultrasound in Medicine, American College of Obstetricians and Gynecologists, American College of Radiology, Society for Pediatric Radiology, and Society of Radiologists in Ultrasound convened a workshop December 13–14, 2012. Workshop participants reviewed indications for ultrasonography and MRI in pregnancy, discussed when and how often these imaging studies should be performed, considered recommendations on the need for additional imaging in certain conditions and in specific patient populations to optimize yield and cost effectiveness, and identified future research opportunities.

FETAL ULTRASOUND

National guidelines regarding obstetric ultrasonography published by various organizations[1–3] highlight the

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The Use of Magnetic Resonance Imaging in the Obstetric Patient

This clinical practice guideline has been prepared by the Diagnostic Imaging Committee, reviewed by the Family Physician Advisory Committee, and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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Abstract

Objective: To review the biological effects and safety of magnetic resonance imaging (MRI) in the obstetric patient and to review procedural issues, indications, and contraindications for obstetrical MRI.

Outcomes: This guideline is intended to reassure patients and clinicians of the safety of MRI in pregnancy and to provide a framework for its use.

Evidence: Published literature was retrieved through searches of PubMed or Medline in 2013 using controlled vocabulary and key words (e.g., MRI, safety, pregnancy). Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies published in English and in French. There were no date restrictions. Searches were updated on a regular basis and incorporated in the guideline to July 2013. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

Values: The quality of evidence in this document was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care (Table).

Benefits, harms, and costs: This article is intended to reassure obstetric care providers that if used in an appropriate manner without the use of contrast agents, MRI in the obstetrical patient is safe for mother and fetus in the second and third trimesters. Because obstetrical MRI is expensive and has limited availability in Canada, this clinical guideline is intended to encourage the judicious use of this resource.

Summary Statements

1. Fetal magnetic resonance imaging is safe at 3.0 tesla or less during the second and third trimesters. (II-2)
2. It is safe to continue breastfeeding after receiving a gadolinium contrast agent. (III)

Recommendations

1. Use of magnetic resonance imaging during the first trimester of pregnancy should be restricted to maternal indications for which the information is considered clinically imperative. Inadvertent exposure to magnetic resonance imaging during the first trimester has not been associated with any long-term sequelae and should not raise clinical concern. (III-C)
2. Gadolinium contrast may be used in pregnant women when the benefits outweigh the potential risks. (III-C)

Keywords: MRI, safety, prenatal diagnosis, indication

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Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*		Classification of recommendations†	
I:	Evidence obtained from at least one properly randomized controlled trial	A.	There is good evidence to recommend the clinical preventive action
II-1:	Evidence from well-designed controlled trials without randomization	B.	There is fair evidence to recommend the clinical preventive action
II-2:	Evidence from well-designed cohort (prospective or retrospective) or case–control studies, preferably from more than one centre or research group	C.	The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3:	Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D.	There is fair evidence to recommend against the clinical preventive action
		E.	There is good evidence to recommend against the clinical preventive action
III:	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	L.	There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.[38]

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.[38]

INTRODUCTION

Ultrasound is currently the standard approach for the initial evaluation of fetal anatomy. It is an imaging modality that is widely available, is cost-effective, and allows real-time examination of the fetus.[1] US has the advantage of providing better spatial resolution than many other imaging techniques including MRI. However, for a variety of reasons, US may not allow adequate assessment of a complex case or provide critical information for antenatal clinical management. MRI can provide additional information resulting in better counselling, management, and perinatal outcomes.[2] This guideline has been developed to discuss safety, pre-procedure counselling, procedural considerations, and indications in the use of obstetrical MRI.

SAFETY OF MRI IN THE OBSTETRICAL PATIENT

Maternal Risks

Maternal risks associated with the use of MRI are the same as for non-pregnant patients.[3,4] One safety consideration for the obstetrical patient is prolonged supine positioning. A gravid uterus of significant size can lead to hypotension due to compression of the inferior vena cava. This can be avoided by placing the patient in a lateral oblique or lateral decubitus position.

Fetal/Neonatal Risks

Theoretical fetal concerns include teratogenic and biological effects. It is known that MRI may cause effects at the cellular level from the induction of local electric fields, currents from static and time-varying magnetic fields, and tissue and cellular heating from RF fields. Most of the biological effects associated with exposure to RF fields are related to thermogenesis. The term "specific absorption rate" refers to the dosimetric absorption of RF power. During an MRI procedure, the SAR is influenced by many complex factors and variables including the strength of the static magnetic field, the type of RF pulse used, the repetition time, the type of transmitting RF coil used and volume of tissue contained within, and the anatomical region exposed, among other factors.[5]

Other physiological, physical, and environmental factors include exposure length, the rate of energy deposition, physiological thermoregulatory response, concomitant illness, and local environmental conditions.[5] Limits are determined for SAR for each pulse sequence to ensure that the increase in body temperature is less than 0.5°C. Maternal and fetal temperatures remain within the specified limits even when sequences with higher SAR values are used, including when SAR increases significantly when using higher magnetic fields.

ABBREVIATIONS

MRI	magnetic resonance imaging
RF	radiofrequency
SAR	specific absorption rate
US	ultrasound

First trimester

Static field exposure has been the subject of animal research. Some animal studies have documented effects on the early fetus in terms of growth, miscarriages, and eye malformations.[6–8] The applicability of these animal models to humans has been questioned.[9] The National Radiological Protection Board in the United Kingdom stipulates in its principles for the protection of patients and volunteers during MRI that it "might be prudent to exclude pregnant woman during the first three months of pregnancy,"[10] whereas the latest American College of Radiology guideline for safe MRI practices does not differentiate among the pregnancy trimesters, and states that all pregnant patients could undergo MRI as long as the benefits outweigh the risks.[11] From a practical standpoint, MRI done during first trimester is usually performed for maternal indications and not for prenatal diagnosis. There are limited case reports of unplanned exposure to MRI in the first trimester of pregnancy. To date there is insufficient evidence to understand the true risks of first trimester exposure to the developing fetus.[8,12] Until these theoretical concerns can be appropriately addressed, we advocate a cautious approach to using obstetrical MRI in the first trimester.

Second and third trimesters

The high level of acoustic noise generated in an MRI system may be of concern for both mother and fetus. The attenuation of sound within the abdomen of a pregnant mother, and its effect on the fetus, is currently under investigation.[9] There are no reports of significant acoustic impairment resulting from exposure to prenatal MRI. Fetal MRI is typically performed at 1.5 T. The higher field strength of 3 T is also considered to be safe.[3] Artifacts may be more pronounced in the second and third trimesters due to the large amount of amniotic fluid and increased abdominal girth.[13] There are no published studies of the long-term effects in human children who have had prenatal exposure at magnetic field strengths of 3 T or more.[14]

Summary Statement

1. Fetal magnetic resonance imaging is safe at 3.0 tesla or less during the second and third trimesters. (II-2)

Recommendation

1. Use of magnetic resonance imaging during the first trimester of pregnancy should be restricted to maternal indications for which the information is considered clinically imperative. Inadvertent exposure to magnetic resonance imaging during the first trimester has not been associated with any long-term sequelae and should not raise clinical concern. (III-C)

Use of contrast agents in obstetrical MRI

Gadolinium is classified as a category C drug by the United States Food and Drug Administration. Intravenous gadolinium is teratogenic in animals at high and repeated doses.[14] Gadolinium crosses the placenta and is excreted by the fetal kidneys into the amniotic fluid, where it remains, exposing the developing fetus, particularly the lungs and gastrointestinal tract, for an extended period of time.[15] The 2010 American College of Radiology guideline for safe MRI practices recommends that intravenous gadolinium be avoided during pregnancy and used only if it is judged absolutely essential. One example of appropriate use could be in an examination for placenta percreta when planned delivery is imminent and fetal exposure to gadolinium is thus limited.[16] The risks and benefits of gadolinium use must be discussed with the pregnant patient and referring clinician.[11] Despite animal data and concerns about the use of gadolinium in pregnancy, there have been no reported adverse human fetal effects.[17] However, many authors remain cautious about the use of gadolinium at any time in pregnancy.[13,18,19]

Recommendation

2. Gadolinium contrast may be used in pregnant women when the benefits outweigh the potential risks. (III-C)

Risks of oral contrast media administration during lactation

In the postnatal period, it may be necessary to perform an MRI for maternal indications and contrast may be used in the lactating mother. A minimal amount of gadolinium is excreted in the breast milk: 99.2% of orally administrated Magnevist (a Gandolinium contrast) is fecally excreted; only 0.1% of the maternal intravenous dose is found in the breast milk, and only 1% of this is subsequently absorbed by the infant.[14] In fact, the 2012 edition of the American College of Radiology manual on contrast media states that "the available data suggest that it is safe for the mother and infant to continue breast-feeding after receiving such an agent."[14] A similar conclusion was reached by the Contrast Media Safety Committee of the European Society of Urogenital Radiology in 2005.[20]

Summary Statement

2. It is safe to continue breastfeeding after receiving a gadolinium contrast agent. (III)

PROCEDURAL CONSIDERATIONS

Obstetrical MRI can be technically challenging to perform and interpret given the movement of the fetus and its variable lie and presentation.

Technical Requirements

The imaging team should consist of:

1. a technologist who fulfills the competency profile of the Canadian Association of Medical Radiation Technologists and has experience in fetal MRI, with specific training in MRI principles, sequences, and safety, and ideally
2. a radiologist who is either trained or highly experienced in fetal MRI.

Standards for credentialing MRI physicians vary from province to province. In British Columbia, subspecialty MRI accreditation (such as fetal MRI), requires 3 months of full-time training. Selection of optimal sequences and interpretation of resulting images requires knowledge of fetal anatomy, pathology, development, and maturation, as well as experience in discriminating between artifacts and true pathology. Fetal MRI is operator-dependent and requires appropriate sequences tailored to the organ system and suspected pathology. The imaging protocol must be altered when the fetus moves or if new anomalies are detected in the course of the scan. In addition to investigating the anomaly in question, the operator should examine the entire fetus and intrauterine structures whenever possible.

Ideally, three orthogonal planes should be obtained through the fetal head and body in each sequence. The MRI protocol primarily includes T2-weighted sequences. T1-weighted, diffusion-weighted, and additional sequences may be added if indicated, and ideally should provide documentation of the entire fetus as well as the placenta, uterus, and surrounding maternal structures. Repeated sequences may be required if the fetus moves. The field of view should be as small as possible without causing foldover artifacts. Slice thickness between 2.5 and 5 mm is used in examining most fetal structures. Thinner slices are possible but have adverse effects on signal-to-noise ratio. At present, the minimum voxel size that may be obtained with fetal MRI is $0.8 \times 0.8 \times 2.5$ mm, with slice thickness and fetal–maternal movement the major limiting factors. These factors decrease resolution and may obscure structures smaller than 1 mm and create difficulties in accurately measuring small or thin structures.

Pre-procedure Counselling

Pre-procedure counselling and education is important prior to obstetrical MRI as it may help alleviate maternal anxiety.[21] Counselling should include discussions of the working diagnosis and the indications for the MRI as well as procedural details, such as the duration of the scan and the noise involved. A communication plan should be formulated to relay information to the patient from the interpreting physician via the primary caregiver as soon as reasonably possible. However, both patient and referring physician should understand that in view of the number of images acquired and the complexity of anatomical data, formulation of an opinion can take many hours and therefore the expectation of a prompt verbal report is in most cases unrealistic.

Maternal and/or Fetal Sedation

Patients may find the claustrophobic environment distressing, particularly if the exam is prolonged by fetal movement and repetitive sequences. In the past, maternal and or fetal sedation was frequently used in obstetrical MRI. With the development of ultrafast sequences, maternal and fetal sedation is no longer required except in extraordinary circumstances.

Technical Considerations

There are limitations in performing fetal MRI in obese patients. With increased body wall thickness, the signal-receiving elements of the coil are not close to the intrauterine regions of interest, and a larger field of view is required; therefore, signal and image resolution are not optimal. A large mother may not fit inside the MRI unit, particularly when placed in decubitus position. Maximum values for body size and weight vary among manufacturers; however, a body circumference of more than 140 cm and/or a weight of more than 140 kg may be problematic.

MRI resolution can also be suboptimal if there are excessive fetal movements. Polyhydramnios can allow increased fetal movement, so should a decompression amniocentesis be performed for other clinical indications, a clinically indicated fetal MRI should be done as soon as reasonably possible following the decompression.

INDICATIONS FOR OBSTETRICAL MRI

US remains the primary diagnostic tool for the fetus, and MRI is an expensive and limited resource in Canada. However, in certain cases MRI may provide additional relevant clinical information that will facilitate perinatal counselling and management decisions.[22]

The indications for fetal MRI cannot be easily defined as they depend on a number of factors including regional differences in perinatal management, experience of technicians and physicians, availability of obstetrical MRI, and access to in-utero fetal surgery. Indications for fetal MRI and technological advances are evolving rapidly and

vary depending on the available expertise and the individual maternal–fetal pathology under investigation.

Central Nervous System

The fetal brain is well-observed on T2-weighted sequences because of the contrast between cerebrospinal fluid and brain tissue. After 17 weeks, the advantages of MRI in diagnoses of both developmental and acquired intracranial abnormalities have been well established[23–25]; however, diagnosis of some abnormalities may not be possible until after 24 weeks. Additional sequences such as T1-weighted and diffusion-weighted imaging provide information about brain development, cell density, myelination, hemorrhage, and ischemic lesions. It should be noted that calcifications are not demonstrated on routine MRI sequences, and consultation with the radiologist is recommended if confirmation of sonographically suspected calcifications is required.

Fetal Oropharynx and Face

MRI can be used to assess oropharyngeal anatomy in conditions where airway patency may be compromised by masses or mandibular or other facial malformations. MRI is useful to confirm or diagnose an isolated cleft of the posterior palate. MRI may also be helpful in clarifying anatomy in other anomalies, such as atypical facial clefts, retrognathia, micrognathia, craniosynostosis, cephaloceles, vascular anomalies, tumours, microphthalmia, and other ocular and orbital abnormalies.[26]

Neck

The position of neck masses relative to the fetal airway can be assessed using MRI, which can assist in managing delivery when an EXIT (ex-utero intrapartum treatment) procedure is being considered. Fetal goiter and thyroid position relative to neck masses can also be imaged on T1- and T2-weighted views.

Thoracic Anomalies

Sonography is the primary screening method for the detection of thoracic anomalies, mediastinal shift, and the presence of fluid in the pleural space. For malformations such as bronchopulmonary sequestration or congenital pulmonary adenomatoid malformation, MRI should be performed if fetal US cannot provide the information necessary for counselling or management.[27] In congenital diaphragmatic hernia, MRI can be used to evaluate lung volume and the presence of liver and intra-abdominal organs in the thorax.[28–30] Pulmonary hypoplasia can be a significant contributor to neonatal mortality and morbidity, and so the antenatal assessment of lung growth and development maybe useful in predicting survival and may aid in perinatal management.

Evaluation of the Fetal Heart

Although sequences are being developed to evaluate cardiac structures and function, fetal echocardiography remains the method of choice for screening and prenatal diagnosis of cardiovascular anomalies.

Intra-abdominal Anomalies

MRI should be reserved for circumstances when fetal US cannot provide the information necessary for counselling or management. After 20 weeks, high signal from meconium on T1-weighted sequences forms the basis for an MRI colonography. This technique can confirm the presence of bowel within the thorax in congenital diaphragmatic hernia, and it can confirm suspected bowel obstruction and anorectal malformations. Calcifications in meconium peritonitis may be depicted sonographically but not on MRI.[31,32]

Urogenital Tract

Urogenital tract structures are readily visualized on US unless severe oligohydramnios or anhydramnios, fetal position, or other condition precludes adequate visualization of anatomy. MRI may be helpful in providing anatomical information in these situations.[33]

Extremities and Bone

US is the primary method of evaluating skeletal biometry and observing findings involving distal appendages. However, sequences have been developed to image musculoskeletal structures with MRI.[34]

Spine

US is the imaging modality of choice to screen for open neural tube defects. MRI can be used to confirm suspected anomalies of the spinal cord.[35]

Maternal Conditions

MRI provides images of maternal anatomy in 3 orthogonal planes without interference from bowel gas. Upper abdominal organs, bowel, kidneys, bladder, ovarian and adnexal masses, uterine anatomy, placental position, and cervical anatomy are visible, and additional targeted sequences can be obtained if necessary. MRI may be particularly useful when appendicitis is suspected clinically and US examination is negative.[36]

Placental Adhesion Disorders

The diagnosis of placental percreta can be made with either US or MRI. However, MRI is the imaging method of choice when there is a risk of posterior placenta increta or percreta.[37]

SUMMARY

Fetal MRI is an expensive and limited resource in Canada. Questions arise over its utility, indications, and safety in

the obstetrical patient. Ultrasound remains the primary diagnostic tool for fetal imaging. Although MRI may provide additional relevant clinical information, fetal movement can create artifacts leading to non-diagnostic images. MRI in the obstetric patient should only be done if the ultrasound assessment is inadequate for antenatal clinical management and the desired information is required in the fetal period; on occasion it may replace neonatal MRI requiring general anaesthesia. MRI should only be performed and interpreted in centres with sufficient expertise following a careful review of all imaging and clinical information. During the first trimester of pregnancy, MRI should be used only as a clinically necessary precaution in the case of theoretical risks. Gadolinium contrast can be used during pregnancy when it can provide critical information for the health of the mother and fetus. Although no documented adverse effects to the human fetus have been documented, gadolinium crosses the placenta and has teratogenic effects in animals. It is safe to breastfeed after receiving a gadolinium contrast agent.

While screening for fetal anomalies and prenatal diagnostic imaging relies primarily on US, fetal MRI tailored to gestational age and suspected pathology has a complementary role in prenatal and perinatal management.

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CPT codes:

78265 Gastric emptying study with small bowel transit
78266 Gastric emptying study with small bowel and colon transit, multiple days

Issue: Gastric emptying study is a standard test for gastroparesis and other stomach motility disorders. Small bowel transit can be studied with barium swallows, wireless capsule endoscopy, breath hydrogen tests, radiopaque marker small bowel transit tests and small intestine scintigraphy. Wireless capsule endoscopy has its own CPT codes. Most small intestinal scintigraphy is coded with CPT 74245 or similar radiology codes.

Similar codes:
74245 (Radiologic examination, gastrointestinal tract, upper; with small intestine, includes multiple serial images) – Diagnostic
78264 (Gastric emptying study) – Diagnostic
78267 and 78268 (urea breath test) – Ancillary
91020 (Gastric motility (manometric) studies) – Diagnostic
91022 (Duodenal motility (manometric) study) – Diagnostic
91110 (Gastrointestinal tract imaging, intraluminal (eg, capsule endoscopy), esophagus through ileum, with interpretation and report) – on lines **32** REGIONAL ENTERITIS, IDIOPATHIC PROCTOCOLITIS, ULCERATION OF INTESTINE and **60** ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE
91111 (Gastrointestinal tract imaging, intraluminal (eg, capsule endoscopy), esophagus with interpretation and report) – Services Recommended for Non-Coverage
91112 (Gastrointestinal transit and pressure measurement, stomach through colon, wireless capsule, with interpretation and report) – Services Recommended for Non-Coverage
91117 (Colon motility (manometric) study, minimum 6 hours continuous recording (including provocation tests, eg, meal, intracolonic balloon distension, pharmacologic agents, if performed), with interpretation and report) – Services Recommended for Non-Coverage

Evidence

1) **AHRQ 2013,** systematic review of gastric and colonic transit studies (PDF not included due to length)
    a. N=12 studies (7 gastric emptying; 9 colonic motility)
    b. Gastric or colonic scintigraphy was used as the "gold standard" test
2) **Szarka 2012**, review of testing for intestinal transit (PDF not included due to length)
    a. **Bariums studies for small intestinal transit:** small bowel transit time measured during barium radiography is inversely related to the volume of the barium administered, and what constitutes a normal barium small bowel transit time remains elusive because of lack of standardization of methods and definitions. In addition, contrast radiography studies provide substantial radiation exposure.
    b. **Radiopaque markers for small intestinal transit:** fairly simple and inexpensive, there may be difficulty in attributing the position of the markers to a specific

anatomical location within the gastrointestinal tract. Additionally, there is substantial radiation exposure with this method.

c. **Scintigraphy for small intestinal transit:** scintigraphy provides physiological and quantitative information. Of the methods reviewed thus far, scintigraphy has yielded the most reliable results. Disadvantages are lack of standardization in clinical practice, lack of general application, the wide range of normal values, and a potential pitfall in interpretation when gastric emptying and/or colonic transit are delayed.
d. **Radiopaque markers for colonic transit:** The advantages of radiopaque marker colon transit tests are the well-established normal values and standardization of methods; it is also readily available and reasonably inexpensive. Disadvantages include the radiation exposure and multiple visits for the 1 to 3 abdominal x-rays that may be required. It is also possible that the solid markers may move through the colon differently than stool. The localization of the markers relative to bone landmarks may not reflect their true position in the colon. These criticisms notwithstanding, the radiopaque markers are the reference standard for colon transit evaluation in clinical practice.
e. **Scintigraphy for colonic transit:** In summary, scintigraphic assessment of colonic transit provides a noninvasive, safe, and relatively rapid (24 or 48 hours) assessment of whole colon and regional colonic transit. The technique is well validated and used in clinical practice and in numerous research studies. Disadvantages include radiation exposure, expense, and the limited availability of radiopharmaceuticals, gamma camera detection equipment, and operator expertise in tertiary medical centers.

Expert guidelines

1) **ACR–SPR 2015,** PRACTICE PARAMETER FOR THE PERFORMANCE OF GASTROINTESTINAL SCINTIGRAPHY (PDF not included due to length)
    a. Combined liquid-phase and solid-phase gastric emptying and small bowel and colon transit studies: A solid-phase examination may be combined with the liquid-phase examination... this combined solid-phase and liquid-phase technique includes the ability to follow the liquid phase to measure small bowel and colon transit resulting in evaluation of the whole gut. There are increasing reports on the utility of whole-gut scintigraphy using simultaneous dual radiopharmaceutical solid-liquid meal in patients with various abdominal symptoms but no consensus recommendations on its use exist to date.
2) **Rao 2011** American and European Neurogastroenterology and Motility Societies position paper on evaluation of gastrointestinal transit (PDF not included due to length)
    a. Breath tests for measurement of intestinal transit: Its shortcomings outweigh its benefits for assessment of small bowel transit in clinical practice.
    b. Scintigraphy: Scintigraphy is recommended for detection of altered small intestinal transit in subjects with suspected diffuse GI motility disorder but is available in a limited number of centers.

c. Wireless capsule endoscopy: The wireless motility capsule (WMC) is a standardized, radiation-free method for assessment of small bowel transit and is recommended for clinical use to facilitate detection of small bowel dysfunction in subjects with a more generalized GI motility disorder
d. No recommendation given on other capsule endoscopy studies (non-WMC)

HERC staff recommendations:

1) Place **78265** (Gastric emptying study with small bowel transit) on the **Diagnostic Procedures File**
    a. Other small bowel motility tests (manography, general radiology tests for upper GI) are Diagnostic
    b. Alternative: Place on the Services Recommended for Non-Coverage Table as it is unclear what imaging modality this code actually represents and there appears to be other CPT codes available that are adequate for most upper intestinal studies
2) Place **78266** (Gastric emptying study with small bowel and colon transit, multiple days) on the **Services Recommended for Non-Coverage Table**
    a. Unclear what testing modalities this new code represents
    b. Colonic motility tests are currently SRNC; therefore follows current code placement
    c. Can re-address if providers request review and can provide further information on these studies
3) HTAS or HERC staff to review all intestinal/colonic transit studies and provide recommendations on which modalities have evidence to support their use and which conditions or symptoms these modalities are able to reliably diagnose or evaluate
    a. Will review wireless capsule endoscopy (CPT 91112) in January, 2016
    b. HERC staff will review placement of 91110 (capsule endoscopy), which is specifically not covered by several insurers and was never formally reviewed prior to adoption on the Prioritized List

2016 Genetic Testing CPT Code Review

81162, 81432-81433 Breast and ovarian cancer syndrome testing

1) 81162: BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis
2) 81432: Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); geonomic sequence analysis panel, must include sequencing of at least 14 genes, including ATM, BRCA1, BRCA2,BRIP1, CDH1, MLH1, MSH2, MSH6, NBN, PALB2, PTEN, RAD51C, STK11 AND TP53
3) 81433: Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer) duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, AND STK1
4) Other BRCA gene testing codes (81211, 81212, 81213) are Diagnostic
    a. These tests are specific gene mutation tests
5) Addressed in the 2015 NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast and Ovarian. V2.2015 (6/25/15)
    a. Recommends multigene testing when more than one gene mutation could explain the family history or when single gene testing is negative in certain clinical situations with genetic counseling input pre and post testing
6) GAP discussion: NCCN guideline contains a table of recommended genetic tests--some of the tests included in the panels above are listed as evidence based, others do not have evidence support. However, the NCCN table has the caveat that even those tests without evidence to support their use might be useful in specific clinical situations. There was discussion about using panel testing versus using customized testing for certain genes. The advisory panel felt that panels are useful in some situations, and the more specific testing might be all that is indicated in other situations. However, the panel tests are frequently the same price as more specific tests. GAP felt that the panel tests above may be more cost effective that singling out the specific tests called out by NCCN as evidence based. Myriad representatives testified that 81432 and 81433 are not priced by Medicare and therefore will likely not be billable for 2016. A miscellaneous genetic testing CPT code will likely to be used instead.
7) HERC staff/GAP recommendation:
    a. Add 81162, 81432-81433 to the **Diagnostic Procedures File**
    b. Add these codes to the relevant section of the non-prenatal genetic testing guideline

2016 Genetic Testing CPT Code Review

81412 Ashkenazi Jewish carrier testing panel

1) 81412: Ashkenazi Jewish associated disorders (eg, Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease), genomic sequence analysis panel must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1 and SMPD1
2) Indicated for use for preconception/early pregnancy testing when both parents are of Asheknazi Jewish ancestry or the spouse is a known Ashkenazi Jewish genetic disorder carrier or when there is a known family history of an Ashkenazi Jewish genetic disorder. Also for use for suspected clinical diagnosis of an individual disorder in a patient
3) The prenatal genetic testing guideline includes coverage for:
    a. #12. Screening for cystic fibrosis carrier status once in a lifetime (CPT 81220-81224)
    b. #15. Screening those with Ashkenazi Jewish heritage for Canavan disease (CPT 81200), familial dysautonomia (CPT 81260), and Tay-Sachs carrier status (CPT 81255)
4) GAP discussion: The group discussed "pan-ethnic" testing, which is becoming increasingly common. These tests are large panels which include genetic defects seen in different genetic groups. "Pan-ethnic" testing is quickly becoming the preferred method to test, due to difficulty in determining a patient's ethnic background, as well as the fact that "pan-ethnic" testing is frequently less expensive than more targeted testing. However, these types of large panel tests have the possibility of finding mutations of questionable significance, or may provide information that the patient/family does not desire to know. There was a question about whether specific Ashkenazi Jewish testing panels will continue to be used, or whether pan-ethnic panels will become the standard.

    The specific use of this test for prenatal testing was discussed in the context of the Prenatal Testing Guideline. This guideline specifically prohibits the use of panels that include tests not specifically approved in the guideline. Based on this wording, GAP felt that the Ashkenazi Jewish panel could not be added to the Prenatal Genetic Testing Guideline. They recommended that this guideline be brought back through the Coverage Guidance process, with specific attention paid to whether larger panel testing should be allowed for all types of prenatal testing as well as specifically for Ashkenazi Jewish patient screening. The Prenatal Genetic Testing Guideline review should also include a discussion about whether pre-conception testing should fall under this guideline or under the non-prenatal genetic testing guideline. Update: after internal discussions, and review of the prenatal genetic testing workgroup deliberations, HERC staff determined that the prenatal genetic testing guideline should be altered to allow Ashenazi Jewish panel testing, if such testing is the same or lower cost as the already

included components of such a panel. Such a panel was not felt to conflict with previous prenatal genetic testing discussions, which had touched on coverage of this specific panel. There was also an equity issue that coverage of Ashkenazi Jewish testing should be the same regardless of whether the testing is done as a preconception test or as part of prenatal testing. The GAP concern about limiting other panel tests for prenatal genetic testing will be brought back to that coverage guidance workgroup when it is convened.

GAP members pointed HERC staff to the American College of Medical Genetics guideline on preconception counseling for information on the probability of each of these types of tests being positive.

The decision was made to cover this test for pre-conception counseling, with restrictions added to the Non-Prenatal Genetic Testing Guideline D1. Update: changes were added to both the prenatal and non-prenatal genetic testing guidelines.

5) HERC staff/GAP recommendation:
    a. Add 81412 to the **Diagnostic Procedures File**
    b. Amend the Non-Prenatal Genetic Testing Guideline and the Prenatal Genetic Testing Guideline to allow testing only when the panel test is used in place of individual tests and is of similar or lower cost than the individual tests.

81434 Hereditary retinal disorders

1) 81434: Hereditary retinal disorders (eg, retinitis pigmentosa, Leber congenital amaurosis, cone-rod dystrophyl, genomic sequence analysis panel, must include sequencing of at least 15 genes, including ABCA4, CNGA1, CRB1, EYS, PDE6A, PDE6B, PRPF31, PRPH2, RDH12, RHO, RP1, RP2, RPE65, RPGR, and USH2A
2) None of these genes currently have specific CPT codes. USH2A is included in a non-symdromic hearing loss panel (CPT 81430)
3) GAP discussion: This appears to be a minimal list of genes to include in a panel; most panels have far more genes. This type of testing influences management significantly.
4) HERC staff/GAP recommendation:
    a. Add 81434 to the **Diagnostic Procedures File**

81437-81438 Hereditary neuroendocrine tumor disorders

1) 81437: Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); genomic sequence analysis panel, must include sequencing of at least 6 genes, including MAX, SDHB, SDHC, SDHD, TMEM127, and VHL

2) 81438: Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma): duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL
3) Gap input: testing is appropriate, will change management or screening
4) HERC staff/GAP recommendation:
    a. Add 81437-81438 to the **Diagnostic Procedures File**

81442 Noonan spectrum disorder testing

1) Noonan spectrum disorders (eg, Noonan Syndrome, cardio -facio - cutaneous syndrome, Costello syndrome, LEOPARD Syndrome, Noonan-like syndrome), genomic sequence analysis panel , must include sequencing of at least 12 genes, including BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1,SHOC2, and SOS1
    a. Lepri 2014
        i. Validation study of multi gene sequencing for Noonan Syndrome
        ii. Conclusion: Here we show how molecular testing of RASopathies by targeted NGS could allow an early and accurate diagnosis for all enrolled patients, enabling a prompt diagnosis, especially for those patients with mild, non-specific or atypical features in whom the detection of the causative mutation usually requires prolonged diagnostic timings when using standard routine. This approach strongly improved genetic counselling and clinical management.
2) GAP discussion: This is an important test to cover. The test will affect management, as some genes affect cancer risk and patients will need surveillance for these cancers if positive. The gene list in this panel is reasonable. The single genetic defect PTPN11 is positive in 50% of kids, but cost difference between this test and whole panel is only about $100. Requiring testing for PTPN11 first, and then the panel if negative, will delay testing and treatment.
3) HERC staff/GAP recommendation:
    a. Add 81442 to the **Diagnostic Procedures File**

Non-Prenatal Genetic Testing Guideline

The non-prenatal genetic testing guideline was reviewed at the October 13, 2015 Genetics Advisory Panel meeting. The following issues were reviewed and the changes below were approved by the GAP members. These issues were raised by GAP members, CCO medical directors, and others during the past year.

Issues:

1) The NCCN guideline references need to be updated
2) OHP medical directors requested that the non-prenatal genetic testing guideline have a section added listing the CPT codes for genetic tests that are currently covered as diagnostic without restrictions
    a. The GAP and HERC staff felt that adding a comprehensive list of covered CPT codes would be too time intensive to be practical and too prone to error. GAP instead recommended adding a clause at the beginning of the guideline noting that all codes not restricted or excluded are diagnostic and covered if they meet the criteria in the guideline
3) HERC staff suggested deleting the genetic testing algorithm and incorporating the intent into the guideline itself
    a. It appears to be unconnected to D1 and difficult to use by the CCOs
4) OHP medical directors requested that the non-prenatal genetic testing guideline list the training requirements for the clinician ordering the genetic test, as well as for the genetic counseling providers. There is concern that OB/Gyns, primary care physicians, and surgeons are ordering tests without appropriate training
    a. GAP did not agree with adding any additional requirements for clinicians ordering these tests. GAP members did not feel that there was an adequate genetic testing workforce for requiring counseling for all testing. Some of these tests are time sensitive and genetic counseling is too long a process. The GAP members felt that there was no good way to specify training required for non-genetic professionals.
5) OHP medical directors requested consideration of adding wording requiring the most cost-effective testing (single test instead of a panel if the panel is not indicated, or panel testing rather than a consecutive series of single tests
    a. An existing clause at end of guideline was moved to the beginning and made to apply to all testing, not just the CPT codes listed in that section.
6) HERC staff have identified discrepancies between the prenatal and non-prenatal genetic testing guidelines sections on CF screening. The prenatal guideline specifies carrier screening will only be done once in a lifetime. Additionally, there were restrictions in the non-prenatal genetic testing guideline for CPT 81224 which were deleted during a review of the CF clauses in June, 2012, apparently by mistake. This code remains diagnostic without any restrictions.

Non-Prenatal Genetic Testing Guideline

HERC staff/GAP recommendations:

1) Modify the non-prenatal genetic testing guideline as shown below
    a. Update the NCCN references
    b. Update the BRCA testing clauses to reflect new CPT codes and the broadening of the spectrum of breast/ovarian cancer syndromes
    c. Move the restriction for the least costly test with required sensitivity from the end of the guideline to the beginning and have apply to all testing
    d. Add a clause recommending that cancer survivors have access to genetic counseling. Genetic testing in this group can influence screening for the same or other cancer conditions (for example, some breast cancer syndromes have a higher risk of colon cancer and require a different colon cancer screening frequency).
    e. Add a clause regarding coverage of Ashkenazi panel testing only when the panel replaces and is of similar/lower cost to individual gene testing
    f. CF section edits
        i. Add a restriction for CF carrier screening to once in a lifetime to bring into agreement with the prenatal genetic testing guideline
        ii. Reinstate previous restrictions on CPT 81224 apparently deleted in error
        iii. Consider adding CPT 81221 (known familial variants) to this section or have GAP address any restrictions on this code at their next meeting
2) Delete the genetic testing algorithm D1 and incorporate the intent into the beginning of the non-prenatal genetic testing guideline
    a. Specify that pre- and post-test genetic counseling is required in most cases
    b. Add a clause that genetic tests not otherwise excluded or restricted are covered if the genetic testing algorithm criteria (as now incorporated into this guideline) are met
3) Discuss modifying the requirement for a 10% change of a genetic abnormality from the guideline. GAP members find that this is a very high bar, as many genetic diseases have a very low probability even in patients with very abnormal physical exams, tests, etc. GAP suggested that “reasonable suspicion” be considered instead.

DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE

~~Coverage of genetic testing in a non-prenatal setting shall be determined by the algorithm shown in Figure C.1 unless otherwise specified below.~~

A) Genetic tests are covered as diagnostic, unless they are listed below in section F1 as excluded or have other restrictions listed in this guideline. To be covered, initial screening (e.g. physical exam, medical history, family history, laboratory studies, imaging studies) must indicate that the chance of genetic abnormality is > 10% and results would do at least one of the following:
   1) Change treatment,
   2) Change health monitoring,
   3) Provide prognosis, or
   4) Provide information needed for genetic counseling for patient; or patient's parents, siblings, or children

B) Pretest and posttest genetic counseling is required for presymptomatic and predisposition genetic testing. Pretest and posttest genetic evaluation (which includes genetic counseling) is covered when provided by a suitable trained health professional with expertise and experience in genetics.
   1) "Suitably trained" is defined as board certified or active candidate status from the American Board of Medical Genetics, American Board of Genetic Counseling, or Genetic Nursing Credentialing Commission.

C) A more expensive genetic test (generally one with a wider scope or more detailed testing) is not covered if a cheaper (smaller scope) test is available and has, in this clinical context, a substantially similar sensitivity. For example, do not cover CFTR gene sequencing as the first test in a person of Northern European Caucasian ancestry because the gene panels are less expensive and provide substantially similar sensitivity in that context.

D) Related to genetic testing for patients with breast/ovarian and colon/endometrial cancer or other related cancers suspected to be hereditary, or patients at increased risk to due to family history.
   1) Services are provided according to the Comprehensive Cancer Network Guidelines.
      a) Lynch syndrome (hereditary colorectal, endometrial and other cancers associated with Lynch syndrome) services (CPT 81288, 81292-81300, 81317-81319, 81435, 81436) and familial adenomatous polyposis (FAP) services (CPT 81201-81203) should be provided as defined by the NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Colorectal V.~~2~~1.201~~4~~5 (~~5/19/14~~ 5/4/15). www.nccn.org.
      b) ~~BRCA1/BRCA2~~ Breast and ovarian cancer syndrome genetic testing services (CPT 81162, 81211-81217, 81432-81433) for women without a personal history of breast, ovarian and other associated cancers should be provided to high risk women as defined by the US Preventive Services Task Force or according to the NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast and Ovarian. V2.201~~4~~5 (~~9/23/2014~~ 6/25/15). www.nccn.org.

c) ~~BRCA1/BRCA2~~ Breast and ovarian cancer syndrome genetic testing services (CPT 81162, 81211-81217, 81432-81433) for women with a personal history of breast, ovarian, and other associated cancers and for men with breast cancer should be provided according to the NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Breast and Ovarian. V2.2014~~4~~5 (~~9/23/2014~~ 6/25/15). www.nccn.org.

d) PTEN (Cowden syndrome) services (CPT 81321-81323) should be provided as defined by the NCCN Clinical Practice Guidelines in Oncology. Colorectal Screening. V.1.2013~~3~~5 (~~5/13/13~~ 5/1/15). www.nccn.org.

2) Genetic counseling should precede genetic testing for hereditary cancer whenever possible.

a) Pre and post-test genetic counseling should be covered when provided by a suitable trained health professional with expertise and experience in cancer genetics. Genetic counseling is recommended for cancer survivors when test results would affect cancer screening.

i) "Suitably trained" is defined as board certified or active candidate status from the American Board of Medical Genetics, American Board of Genetic Counseling, or Genetic Nursing Credentialing Commission.

b) If timely pre-test genetic counseling is not possible for time-sensitive cases, appropriate genetic testing accompanied by pre- and post- test informed consent and post-test disclosure performed by a board-certified physician with experience in cancer genetics should be covered.

i) Post-test genetic counseling should be performed as soon as is practical.

3) If the mutation in the family is known, only the test for that mutation is covered. For example, if a mutation for BRCA 1 has been identified in a family, a single site mutation analysis for that mutation is covered (CPT 81215), while a full sequence BRCA 1 and 2 (CPT 81211) analyses is not. There is one exception, for individuals of Ashkenazi Jewish ancestry with a known mutation in the family, the panel for Ashkenazi Jewish BRCA mutations is covered (CPT 81212).

4) Costs for rush genetic testing for hereditary breast/ovarian and colon/endometrial cancer is not covered.

E) Related to diagnostic evaluation of individuals with intellectual disability (defined as a full scale or verbal IQ < 70 in an individual > age 5), developmental delay (defined as a cognitive index <70 on a standardized test appropriate for children < 5 years of age), Autism Spectrum Disorder, or multiple congenital anomalies:

1) CPT 81228, Cytogenomic constitutional microarray analysis for copy number variants for chromosomal abnormalities: Cover for diagnostic evaluation of individuals with intellectual disability/developmental delay; multiple congenital anomalies; or, Autism Spectrum Disorder accompanied by at least one of the following: dysmorphic features including macro or microcephaly, congenital anomalies, or intellectual disability/developmental delay in addition to those required to diagnose Autism Spectrum Disorder.

2) CPT 81229, Cytogenomic constitutional microarray analysis for copy number variants for chromosomal abnormalities; plus cytogenetic constitutional microarray analysis

for single nucleotide polymorphism (SNP) variants for chromosomal abnormalities: Cover for diagnostic evaluation of individuals with intellectual disability/developmental delay; multiple congenital anomalies; or, Autism Spectrum Disorder accompanied by at least one of the following: dysmorphic features including macro or microcephaly, congenital anomalies, or intellectual disability/developmental delay in addition to those required to diagnose Autism Spectrum Disorder; only if (a) consanguinity and recessive disease is suspected, or (b) uniparental disomy is suspected, or (c) another mechanism is suspected that is not detected by the copy number variant test alone.

3) CPT 81243, 81244, Fragile X genetic testing is covered for individuals with intellectual disability/developmental delay. Although the yield of Fragile X is 3.5-10%, this is included because of additional reproductive implications.
4) A visit with the appropriate specialist (often genetics, developmental pediatrics, or child neurology), including physical exam, medical history, and family history is covered. Physical exam, medical history, and family history by the appropriate specialist, prior to any genetic testing is often the most cost-effective strategy and is encouraged.

F) Related to other tests with specific CPT codes:
1) The following tests are not covered:
a) CPT 81225, CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)
b) CPT 81226, CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN).
c) CPT 81227, CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)
d) CPT 81287, MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme), methylation analysis
e) CPT 81291, MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
f) CPT 81330, SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)
g) CPT 81350, UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, irinotecan metabolism), gene analysis, common variants (eg, *28, *36, *37)
h) CPT 81355, VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variants (eg, -1639/3673)
i) CPT 81417, re-evaluation of whole exome sequencing
j) CPT 81425-81427, Genome sequence analysis
k) CPT 81470, 81471, X-linked intellectual disability (XLID) genomic sequence panels
l) CPT 81504, Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores

2) The following tests are covered only if they meet the criteria in section A above ~~for the Non-Prenatal Genetic Testing Algorithm~~ AND the specified situations:
   a) CPT 81205, BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, Maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X): Cover only when the newborn screening test is abnormal and serum amino acids are normal
   b) Diagnostic testing for cystic fibrosis (CF)
      i) CFTR, cystic fibrosis transmembrane conductance regulator tests. CPT 81220, 81223, 81222: For infants with a positive newborn screen for cystic fibrosis or who are symptomatic for cystic fibrosis, or for clients that have previously been diagnosed with cystic fibrosis but have not had genetic testing, CFTR gene analysis of a panel containing at least the mutations recommended by the American College of Medical Genetics* (CPT 81220) is covered. If two mutations are not identified, CFTR full gene sequencing (CPT 81223) is covered. If two mutations are still not identified, duplication/deletion testing (CPT 81222) is covered. These tests may be ordered as reflex testing on the same specimen.
   c) Carrier testing for cystic fibrosis
      i) CFTR gene analysis of a panel containing at least the mutations recommended by the American College of Medical Genetics* (CPT 81220) is covered once in a lifetime.
   d) CPT 81224, CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; intron 8 poly-T analysis (eg, male infertility): Covered only after genetic counseling.
   e) CPT 81240. F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant: Factor 2 20210G>A testing should not be covered for adults with idiopathic venous thromoboembolism; for asymptomatic family members of patients with venous thromboembolism and a Factor V Leiden or Prothrombin 20210G>A mutation; or for determining the etiology of recurrent fetal loss or placental abruption.
   f) CPT 81241. F5 (coagulation Factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant: Factor V Leiden testing should not be covered for: adults with idiopathic venous thromoboembolism; for asymptomatic family members of patients with venous thromboembolism and a Factor V Leiden or Prothrombin 20210G>A mutation; or for determining the etiology of recurrent fetal loss or placental abruption.
   g) CPT 81256, HFE (hemochromatosis) (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D): Covered for diagnostic testing of patients with elevated transferrin saturation or ferritin levels. Covered for predictive testing ONLY when a first degree family member has treatable iron overload from HFE.
   h) CPT 81332 SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z): The alpha-1-antitrypsin protein level should be

the first line test for a suspected diagnosis of AAT deficiency in symptomatic individuals with unexplained liver disease or obstructive lung disease that is not asthma or in a middle age individual with unexplained dyspnea. Generic testing or the anpha-1 phenotype test is appropriate is the protein test is abnormal or borderline. The genetic test is appropriate for siblings of people with AAT deficiency regardless of the AAT protein test results.

i) CPT 81415-81416, exome testing: A genetic counseling/geneticist consultation is required prior to ordering test

j) CPT 81430-81431, Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel: Testing for mutations in GJB2 and GJB6 need to be done first and be negative in non-syndromic patients prior to panel testing.

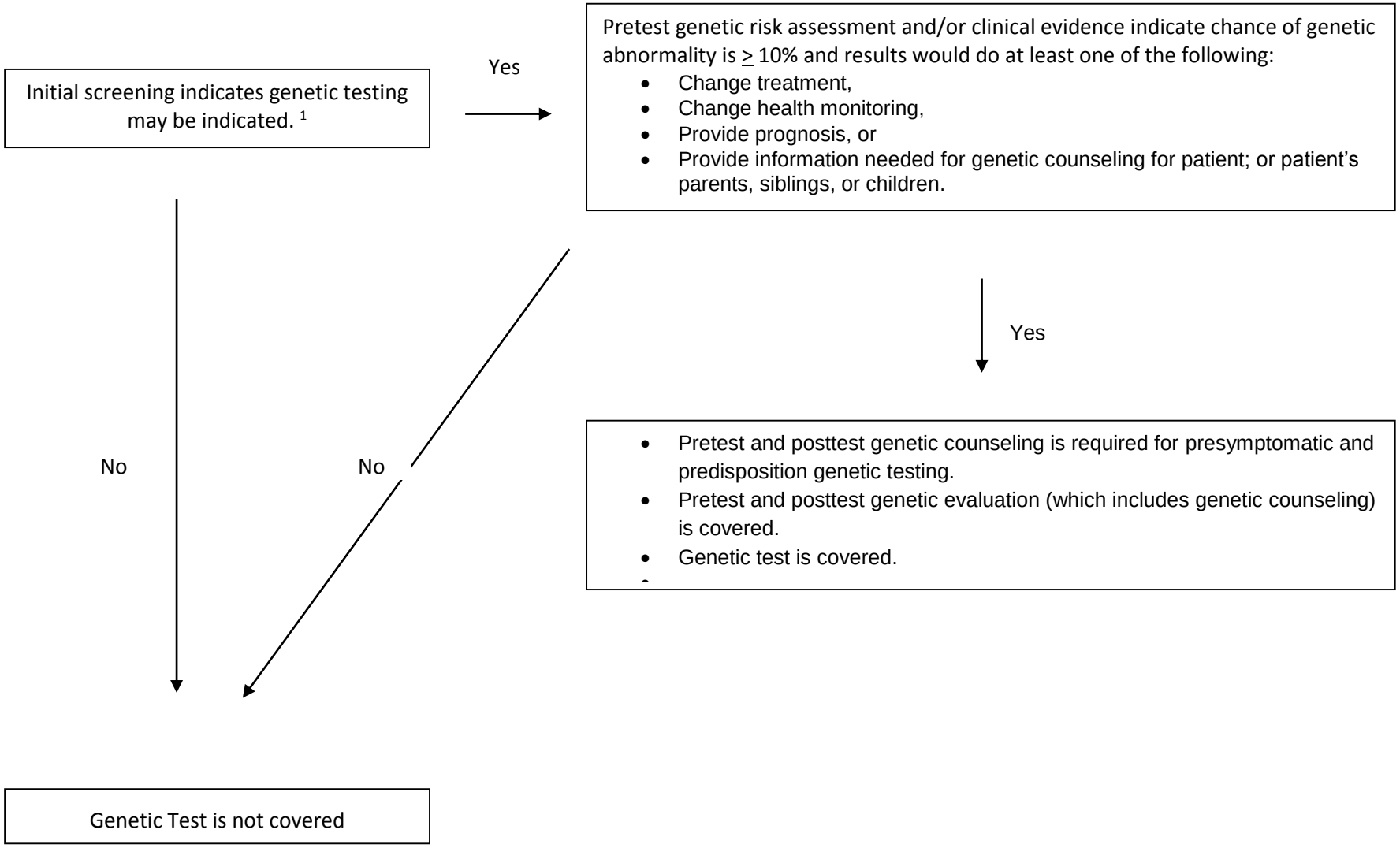
k) CPT 81440, 81460, 81465, mitochondrial genome testing: A genetic counseling/geneticist or metabolic consultation is required prior to ordering test.

l) 81412 Ashkenazi Jewish carrier testing panel: panel testing is only covered when the panel would replace and would be of similar or lower cost than individual gene testing including CF carrier testing.

~~m) Do not cover a more expensive genetic test (generally one with a wider scope or more detailed testing) if a cheaper (smaller scope) test is available and has, in this clinical context, a substantially similar sensitivity. For example, do not cover CFTR gene sequencing as the first test in a person of Northern European Caucasian ancestry because the gene panels are less expensive and provide substantially similar sensitivity in that context.~~

* American College of Medical Genetics Standards and Guidelines for Clinical Genetics Laboratories. 2008 Edition, Revised 3/2011 and found at https://www.acmg.net/StaticContent/SGs/CFTR%20Mutation%20Testing.pdf

FIGURE D1
NON-PRENATAL GENETIC TESTING ALGORITHM (See Guideline Note D1)



1. Examples of initial screening: physical exam, medical history, family history, laboratory studies, imaging studies.

PRENATAL GENETIC TESTING GUIDELINE

The Genetics Advisory Panel meeting and subsequent staff review has found several issues with the prenatal genetic testing guideline tht need to be addressed.

1) The Ashkenazi Jewish testing section should be modified to agree with the non-prenatal genetic testing guideline
2) The CF testing section should have 2 CPT codes deleted. These codes are used for the diagnostic testing for suspected CF cases, not for genetic carrier screening.
    a. 81220 is the general CF carrier screening test, 81221 is the test for patients with known familial mutations
    b. 81222 (duplication/deletion variants) and 81223 (full gene sequence) are used only for the work up of suspected CF and are 3rd line and 2nd line testing respectively

DIAGNOSTIC GUIDELINE D17, PRENATAL GENETIC TESTING

The following types of prenatal genetic testing and genetic counseling are covered for pregnant women:

1. Genetic counseling (CPT 96040, HPCPS S0265) for high risk women who have family history of inheritable disorder or carrier state, ultrasound abnormality, previous pregnancy with aneuploidy, or elevated risk of neural tube defect.
2. Genetic counseling (CPT 96040, HPCPS S0265) prior to consideration of CVS, amniocentesis, microarray testing, Fragile X, and spinal muscular atrophy screening
3. Validated questionnaire to assess genetic risk in all pregnant women
4. Screening high risk ethnic groups for hemoglobinopathies (CPT 83020, 83021)
5. Screening for aneuploidy with any of five screening strategies [first trimester (nuchal translucency, beta-HCG and PAPP-A), integrated, serum integrated, stepwise sequential, and contingency] (CPT 76813, 76814, 81508-81511)
6. Cell free fetal DNA testing (CPT 81507) for evaluation of aneuploidy in women who have an elevated risk of a fetus with aneuploidy (maternal age >34, family history or elevated risk based on screening).
7. Ultrasound for structural anomalies between 18 and 20 weeks gestation (CPT 76811, 76812)
8. CVS or amniocentesis (CPT 59000, 59015) for a positive aneuploidy screen, maternal age >34, fetal structural anomalies, family history of inheritable chromosomal disorder or elevated risk of neural tube defect.
9. Array CGH (CPT 81228) when major fetal congenital anomalies apparent on imaging, and karyotype is normal
10. FISH testing (CPT 88271, 88275) only if karyotyping is not possible due a need for rapid turnaround for reasons of reproductive decision-making (i.e. at 22w4d gestation or beyond)
11. Screening for Tay-Sachs carrier status (CPT 81255) in high risk populations. First step is hex A, and then additional DNA analysis in individuals with ambiguous Hex A test results, suspected variant form of TSD or suspected pseudodeficiency of Hex A
12. Screening for cystic fibrosis carrier status once in a lifetime (CPT 81220-8122~~2~~4)

13. Screening for fragile X status (CPT 81243, 81244) in patients with a personal or family history of
    a. fragile X tremor/ataxia syndrome
    b. premature ovarian failure
    c. unexplained early onset intellectual disability
    d. fragile X intellectual disability
    e. unexplained autism through the pregnant woman's maternal line
14. Screening for spinal muscular atrophy (CPT 81401) once in a lifetime
15. Screening those with Ashkenazi Jewish heritage for Canavan disease (CPT 81200), familial dysautonomia (CPT 81260), and Tay-Sachs carrier status (CPT 81255). Ashkenazi Jewish carrier panel testing (CPT 81412) is covered if the panel would replace and would be of similar or lower cost than individual gene testing including CF carrier testing.
16. Expanded carrier screening only for those genetic conditions identified above

The following genetic screening tests are not covered:

1. Serum triple screen
2. Screening for thrombophilia in the general population or for recurrent pregnancy loss
3. Expanded carrier screening which includes results for conditions not explicitly recommended for coverage

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/herc/Pages/blog-prenatal-genetic.aspx

2016 CPT Code Review
Cancer Genetic Testing

81170 ABL 1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (eg, acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain

1) Definition: BCR-ABL mutation analysis is a basic diagnostic test for acute lymphoblastic and chronic myelogenous leukemia (ALL and CML), which has a separate set of CPT codes (81206-81208). The ABL1 mutation test represented by this CPT code has been suggested as a test to determine whether the patient has developed resistance to the first line chemotherapy agent (tyrosine kinase inhibitors).
2) Similar codes:
    a. 81206-81208 (BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis, major/minor/other breakpoint) are currently DMAP Diagnostic Procedure File
        i. These CPT codes are NOT tumor markers, but part of the basic diagnostic work up for CML
3) Expert guidelines
    a. NCCN 2015 Chronic Myelogenous Leukemia Treatment
        i. BCR/ABL1 positive/negative is the first branchpoint in the treatment algorithm.
        ii. ABL1 tyrosine kinase testing is not mentioned
4) Expert input
    a. Dr. Gregory Thomas, OHSU Pediatric Oncoogy: Presence of mutations associated with Imatinib resistance would change therapy in CML. I…recommend coverage
5) HERC staff recommendation:
    a. Add CPT 81170 to the **Diagnostic Workup File** until HTAS review of cancer genetic markers in 2016

81218 CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha)(eg, acute myeloid leukemia), gene analysis, full gene sequence

1) Definition: gene mutation that is associated with acute myeloid leukemia.
2) Expert guidelines
    a. NCCN 2015 guideline for treatment of AML
        i. Recommends testing for KIT, LFT3-ITD, NPM1 and CEBPA mutations as work up for acute myeloid leukemia. These mutations are important for prognostication in a subset of patients (category 2A) and may guide therapeutic interventions (category 2B)
3) HERC staff recommendation:
    a. Add CPT 81218 to the **Diagnostic Workup File** until HTAS review in 2016

2016 CPT Code Review
Cancer Genetic Testing

81219 CALR (calreticulin)(eg, myeloproliferative disorders), gene analysis, common variants in exon 9

1) Expert guidelines
    a. NCCN 2015 CML
        i. Mentions CALR testing as possibly assisting in making a diagnosis for BCR/ABL1 negative tumors, for example, determining if the cancer is essential thrombocythemia, primary myelofibrosis or polycythemia vera.
2) HERC staff recommendation:
    a. Add CPT 81219 to the **Services Recommended for Non-Coverage Table** until HTAS tumor marker review in 2016

81272 KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog)(eg, gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (eg, exons 8, 11, 13, 17, 18,)

1) Expert guidelines
    a. NCCN 2015 guideline for treatment of AML
        i. Recommends testing for KIT, LFT3-ITD, NPM1 and CEBPA mutations as work up for acute myeloid leukemia. These mutations are important for prognostication in a subset of patients (category 2A) and may guide therapeutic interventions (category 2B)
    b. NCCN 2015 guideline for treatment of melanoma
        ii. KIT testing recommended as an option for patients with poor initial prognosis or patients with disease progression despite appropriate therapy who have metastatic or unresectable disease
    c. **NCCN 2015** guideline for treatment of soft tissue sarcoma (GIST section)
        iii. KIT and PDGFRA mutation testing is strongly recommended at initial presentation of GIST. The mutation types for these genes are used for selection of chemotherapy agents and therefore the test would result in a change in treatment
4) HERC staff recommendation:
    a. Add CPT 81272 to the **Diagnostic Workup File** until HTAS review in 2016

2016 CPT Code Review
Cancer Genetic Testing

81273 KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, mastocytosis, gene analysis, D816 variant(s)

1) Definition: a genetic test used for the evaluation of mastocytosis, group of hematopoietic malignancies characterized by excessive proliferation of neoplastic mast cells that accumulate in the skin, and in systemic cases in the bone marrow and visceral organs
2) Other policies: no NCCN guidelines found
3) Lines with relevant diagnoses:
    a. 162 NON-HODGKIN'S LYMPHOMAS (contains C96.2 Malignant mast cell tumor)
    b. 660 DERMATOLOGICAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY (contains Q82.2 Mastocytosis)
4) HERC staff recommendation:
    a. Place 81273 on the **Services Recommended for Non-Coverage Table** until 2016 HTAS review

Colon cancer genetic testing

1) CPT codes:
    a. **81276** KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (eg, carcinoma) gene analysis additional variants(s) (eg, codon 61, codon 146)
    b. **81311** NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (eg, colorectal carcinoma), gene analysis, variants in exon 2 (eg, codons 12 and 13) and exon 3 (eg, codon 61)
1) Definition: genetic tests on colon cancer tissue used to assist in determination of chemotherapy choice
2) Other policies
    a. **NCCN 2015** Colon Cancer Treatment
        i. Work up should include determination of tumor gene status for RAS (KRAS exon 2 and non-exon 2, and NRAS) and BRAF
        ii. Gene status determines choice of chemotherapy agents
    b. **NCCN 2011** Review of tumor markers in oncology
        i. KRAS mutations in codons 12 and 13 reviewed
        ii. Mutations in codons 61 and 146 not mentioned
3) Similar codes:
    a. 81275 (KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (eg, carcinoma) gene analysis, variants in codons 12 and 13) is on colon cancer line based on a 2015 HTAS Coverage Guidance review.
4) Expert input
    a. Dr. Gerry Ahman: The clinical significance of NRAS in humans is less clear and I would not pay for its screening

5) HERC staff recommendations:
    a. Place 81276 (KRAS) on the **Diagnostic Workup File** until HTAS review in 2016
    b. Place 81311 (NRAS) on the **Services Recommended for Non-Coverage Table** until HTAS review in 2016

81314 PDGFRA (platelet-derived growth factor receptor, alpha polypeptide) (eg, gastrointestinal stromal tumor [GIST],gene analysis, targeted sequence analysis (eg, exons 12, 18)

1) Expert guidelines
    a. **NCCN 2015** guideline for treatment of soft tissue sarcoma (GIST section)
        i. KIT and PDGFRA mutation testing is strongly recommended at initial presentation of GIST. The mutation types for these genes are used for selection of chemotherapy agents and therefore the test would result in a change in treatment

5) HERC staff recommendation:
    a. Add CPT 81314 to the **Diagnostic Workup File** until HTAS review in 2016

Algorithmic oncology tests

1) CPT codes:
    a. **81525** Oncology (colon), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence score
    b. **81528** Oncology (colorectal) screening, quantitative real-time target and signal amplification of 10 DNA markers (KRAS mutations, promoter methylation of NDRG4 and BMP3) and fecal hemoglobin, utilizing stool, algorithm reported as a positive or negative result
        i. Reviewed in the **NCCN 2015** colorectal cancer screening guideline. Not recommended for routine screening at this time.
    c. **81535-81536** Oncology (gynecologic), live tumor cell culture and chemotherapeutic response by DAPI stain and morphology, predictive algorithm reported as a drug response score
    d. **81538** Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm, reported as good versus poor overall survival
    e. **81540** Oncology (tumor of unknown origin), mRNA, gene expression profiling by real-time RT-PCR of 92 genes (87 content and 5 housekeeping) to classify tumor into main cancer type and subtype, utilizing formalin-fixed paraffin-embedded

tissue , algorithm reported as a probability of a predicted main cancer type and subtype

f. **81545** Oncology (thyroid), gene expression analysis of 142 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (eg, benign or suspicious)

2) Definition: these oncology gene testing algorithms are proprietary tests (for example, 81545 refers to the Afirma® Gene Expression Classifier) which can be used to help determine prognostic or diagnostic features of a cancer, or may help determine drug selection.
3) Other coverage: Most major insurers are not covering these tests. NCCN does not mention these tests specifically in their various guidelines.
4) HERC staff recommendations:
    a. Place 81535, 81528, 81535, 81536, 81538, 81540, 81545 and 81595 on the **Services Recommended for Non-Coverage Table** until the 2016 HTAS cancer genetic marker review

81490

1) Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score
2) Evidence
    a. **Centola 2015** http://www.ncbi.nlm.nih.gov/pubmed/23585841 (not included in packet due to study's length)
        i. Development of the 12 biomarker algorithm
        ii. Multibiomarker statistical models outperformed individual biomarkers at estimating disease activity. Biomarker-based scores were significantly correlated with DAS28-CRP and could discriminate patients with low vs. moderate/high clinical disease activity. Such scores were also able to track changes in DAS28-CRP and were significantly associated with both joint inflammation measured by ultrasound and damage progression measured by radiography. The final multibiomarker disease activity (MBDA) algorithm uses 12 biomarkers to generate an MBDA score between 1 and 100. No significant effects on the MBDA score were found for common comorbidities.
        iii. Conclusion: We followed a stepwise approach to develop a quantitative serum-based measure of rheumatoid arthritis (RA) disease activity, based on 12-biomarkers, which was consistently associated with clinical disease activity levels.
    b. **Michaud 2015** http://www.ncbi.nlm.nih.gov/pubmed/25877911 (not included in packet due to study's length)
        i. Study of the RA MBDA blood test on clinical progression and cost of treatment
        ii. Use of the MBDA test is projected to improve health assessment questionnaire (HAQ) scores by 0.09 units in year 1, declining to 0.02 units after 10 years. Over the 10 year time horizon, quality-adjusted life years increased by 0.08 years and costs decreased by US$457 (cost savings in disability-related medical costs, US$659; in productivity costs, US$2137). The most influential variable in the analysis was the effect of the MBDA test on clinician treatment recommendations and subsequent HAQ changes.
        iii. Conclusion. The MBDA test aids in the assessment of disease activity in patients with RA by changing treatment decisions, improving the functional status of patients and cost savings. Further validation is ongoing and future longitudinal studies are warranted.
    c. **Hambardzumyan 2015** http://www.ncbi.nlm.nih.gov/pubmed/24812287 (not included in packet due to study's length)
        i. Study of MBDA score, based on 12 serum biomarkers as a baseline predictor for 1-year rheumatoid progression (RP) in early RA

ii. MBDA score was an independent predictor of RP as a continuous (OR=1.05, 95% CI 1.02 to 1.08) and dichotomised variable (high versus low/moderate, OR=3.86, 95% CI 1.04 to 14.26).
iii. Conclusions: In patients with early RA, the MBDA score at baseline was a strong independent predictor of 1-year RP. These results suggest that when choosing initial treatment in early RA the MBDA test may be clinically useful to identify a subgroup of patients at low risk of RP.

3) Summary: test is in the development stage, with clinical utility still being determined
4) HERC staff recommendation:
    a. Add 81490 to the **Services Recommended for Non-Coverage Table**
        i. Experimental

81493

1) Coronary artery disease, mRNA, gene expression profiling by real-time RT-PRC of 23 genes, utilizing whole peripheral blood, algorithm reported as a risk score
2) Proprietary algorithm test which can help predict whether a patient's symptoms are due to obstructive coronary artery disease
3) Evidence
    a. Rosenberg 2010 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3786733/ (not included in packet due to study's length)
        i. Validation study
        ii. N=526 non-diabetic patients clinically indicated for invasive coronary angiography
            1. excluded patients with chronic inflammatory disorders, elevated white blood counts or cardiac protein markers, and diabetes.
        i. Results: At a score threshold corresponding to 20% obstructive coronary artery disease (oCAD) likelihood (14.75), the sensitivity and specificity were 85% and 43%, yielding NPV of 83% and PPV 46%, with 33% of patient scores below this threshold.
        ii. Conclusions: This non-invasive whole blood test, based on gene expression and demographics, may be useful for assessment of obstructive CAD in non-diabetic patients without known CAD.
    b. Phelps 2015 http://www.ncbi.nlm.nih.gov/pubmed/24766980 (not included in packet due to study's length)
        i. Cost effectiveness modeling for mRNA algorithm for CAD
        ii. the 2-threshold gene expression score (GES) strategy is the most cost-effective strategy at a threshold of $100,000 per QALY gained, with an ICER of approximately $72,000 per QALY gained relative to no testing. Myocardial perfusion imaging alone and the 1-threshold strategy are weakly dominated. In sensitivity analysis, ICERs fall as the probability of oCAD increases from the base case value of 15%. The ranking of

ICERs among strategies is sensitive to test costs, including the time cost for testing. The analysis reveals ways to improve on pre-specified GES thresholds.

iii. Conclusions: Diagnostic testing for oCAD with a novel GES strategy in a 2-threshold model is cost effective by conventional standards. This diagnostic approach is more efficient than usual care of myocardial perfusion imaging alone or a 1-threshold GES strategy in most scenarios.

4) Summary: test is in the development stage, with clinical utility still being determined
5) HERC staff recommendation:
    a. Add 81493 to the **Services Recommended for Non-Coverage Table**
        i. Experimental

81595

1) Cardiology (heart transplant), mRNA, gene expression profiling by real-time quantitative PCR of 20 genes (11 content and 9 housekeeping), utilizing subfraction of peripheral blood, algorithm reported as rejection risk score
2) Proprietary genetic test (AlloMap). AlloMap testing is intended to aid in the identification of heart transplant recipients who have a low probability of moderate/severe acute cellular rejection (ACR) at the time of testing.
3) Evidence
    a. **CTAF 2010** review http://ctaf.org/sites/default/files/assessments/1208_file_AlloMap_2010_W.pdf (not included in packet due to study's length)
        i. The AlloMap gene expression profile has a high negative predictive value, but a low positive predictive value. Thus it may be useful to avoid biopsy in stable patients, but the high false positive rate precludes its use to definitively diagnose acute cellular rejection. Endomyocardial biopsies will still need to be performed in all patients with elevated AlloMap scores and all patients with clinical signs of rejection.
        ii. the data only support strategies utilizing AlloMap in patients more than a year post-transplant.
        iii. **RECOMMENDATION** It is recommended that the use of gene expression profiling meets Technology Assessment Criterion 1 through 5 for safety, effectiveness and improvement in health outcomes when used to manage heart transplant patients at least one year post-transplant.
4) Other policies
    a. **Anthem BCBS 2015:** AlloMap molecular expression testing is considered medically necessary as a non-invasive method of determining the risk of rejection in heart transplant recipients between 1 and 5 years post-transplant.

b. **Aetna 2015:** **http://www.aetna.com/cpb/medical/data/500_599/0586.html** (not included in packet due to length) Aetna considers the Allomap gene expression profile medically necessary for monitoring rejection in heart transplant recipients more than six months post-heart transplant.

5) HERC staff recommendations:
   a. Add 81595 (Cardiology (heart transplant), mRNA, gene expression profiling) to the heart transplant lines
      i. **245** CONDITIONS REQUIRING HEART-LUNG AND LUNG TRANSPLANTATION
      ii. **268** CONGESTIVE HEART FAILURE, CARDIOMYOPATHY, MALIGNANT ARRHYTHMIAS, AND COMPLEX CONGENITAL HEART DISEASE
   b. Add a new guideline to lines 245 and 268

GUIDELINE NOTE XXX, CARDIAC TRANSPLANT GENETIC TESTING FOR TRANSPLANT REJECTION

Lines 245,268

Genetic testing for cardiac transplant rejection (CPT 81595) is included on these lines only for patients at least 1 year post transplant who are without clinical signs of rejection.

Medical Policy

Subject:	Laboratory Testing as an Aid in the Diagnosis of Heart Transplant Rejection		
Policy #:	TRANS.00025	**Current Effective Date:**	07/07/2015
Status:	Reviewed	**Last Review Date:**	05/07/2015

Description/Scope

This document addresses specific noninvasive laboratory tests for the early detection of rejection following a heart transplant. This includes the Heartsbreath test (Menssana Research, Inc. Fort Lee, NJ), which measures the chemical byproducts of allograft rejection and has been investigated to potentially make the process of monitoring heart transplant recipients safer and less complicated. Also addressed in this document is the AlloMap® molecular expression testing (XDx, Inc., South San Francisco, CA) which has also been investigated as a noninvasive method of determining the risk of rejection in heart transplant recipients.

Even with modern drug therapy, rejection remains a constant hazard, and transplant recipients must be tested repeatedly for signs of renewed rejection. Currently, the gold standard to detect heart transplant rejection is endomyocardial biopsy. This is typically performed weekly for the first 6 weeks, biweekly until the third month, monthly to 6 months and then every 1 to 3 months, as indicated.

Position Statement

Medically Necessary:

AlloMap molecular expression testing is considered **medically necessary** as a non-invasive method of determining the risk of rejection in heart transplant recipients between 1 and 5 years post-transplant.

Investigational and Not Medically Necessary:

Breath testing with the Heartsbreath test is considered **investigational and not medically necessary** for use as an aid in the diagnosis of heart transplant rejection.

AlloMap molecular expression testing is considered **investigational and not medically necessary** when the criteria above are not met.

Rationale

Breath Test

Heartsbreath (Breath test for Grade 3 heart transplant rejection), manufactured by Menssana Research, Inc., (Fort Lee, NJ) received U.S. Food and Drug Administration (FDA) clearance on February 24, 2004 under the Humanitarian Device Exemption (HDE)* program with the following indications for use:

> The Heartsbreath test is indicated for use as an aid in the diagnosis of grade 3 heart transplant rejection in patients who have received heart transplants within the preceding year. The Heartsbreath test is intended for use as an adjunct to, and not as a substitute for, endomyocardial biopsy. The use of the device is limited to patients who have had endomyocardial biopsy (EMB) within the previous month (FDA, 2004).

The Heartsbreath test works on the principle that rejection of the transplanted heart is accompanied by oxidative stress that degrades membrane polyunsaturated fatty acids, evolving alkanes and methylalkanes that are excreted in the breath as volatile organic compounds (VOCs). The individual breathes for 2 minutes through a disposable mouthpiece attached to a breath collecting device, which then analyzes the VOCs in alveolar and room air and interprets the values, using a proprietary algorithm to predict the probability of Grade 3 heart transplant rejection.

The Heartsbreath test should not be used for individuals who have received a heart transplant more than 1 year ago, or have a Grade 4 heart transplant rejection, because Heartsbreath has not been evaluated in these groups.

FDA clearance was based on the results of the Heart Allograft Rejection: Detection with Breath Alkanes in Low Levels (HARDBALL) Study, which was sponsored by the National Heart Lung and Blood Institute. In this 3 year multicenter study, investigators evaluated a new marker of heart transplant rejection, the breath methylated alkane contour (BMAC). In the HARDBALL study, 1061 breath VOC samples were collected from 539 heart transplant recipients at seven sites on the day of scheduled EMB. The gold standard of rejection was the concordant set of International Society for Heart and Lung Transplantation (ISHLT) grades in biopsies read by two cardiac pathologists. Results included concordant biopsies of:

- Grade 0, 645 of 1061 (60.8%);
- Grade 1A, 197 (18.6%);
- Grade 1B, 84 (7.9%);
- Grade 2, 93 (8.8%);
- Grade 3A, 42 (4.0%).

A combination of 9 VOCs in the BMAC identified Grade 3 rejection (sensitivity 78.6%; specificity 62.4%; cross-validated sensitivity 59.5%; cross-validated specificity 58.8%; positive predictive value 5.6%; negative predictive value 97.2%). Site pathologists identified the same cases with sensitivity of 42.4%, specificity 97.0%, positive predictive value 45.2% and negative predictive value 96.7%. The authors concluded that a breath test for markers of oxidative stress was more sensitive and less specific for Grade 3 heart transplant rejection than a biopsy reading by a single on-site pathologist, but the negative predictive values of the two tests were similar. They concluded that a negative screening breath test could potentially identify transplant recipients at low risk of Grade 3 rejection and obviate the need for EMB in this group, thereby reducing the overall number of EMBs performed, which was estimated to be by as much as 50% (Phillips, 2004).

Currently, there is inadequate evidence in the published literature to demonstrate the safety, efficacy, and clinical utility of the Heartsbreath test in the management of rejection surveillance following heart transplant. Large trials are needed to further define the role of this technology and demonstrate how use of this test will impact treatment management.

AlloMap Molecular Expression Testing

The AlloMapmolecular expression blood test was developed by XDx, Inc. (South San Francisco, CA). In 2008, FDA 510(k) clearance as a Class II approval was granted for AlloMap Molecular Expression Testing as an in-vitro, diagnostic, multivariate, index assay test service, which assesses the gene expression profile of RNA isolated from peripheral blood mononuclear cells for the following indication:

> To aid in the identification of heart transplant recipients with stable allograft function who have a low probability of moderate/severe acute cellular rejection (ACR) at the time of testing in conjunction with standard clinical assessment. AlloMap is indicated for use in heart transplant recipients who are 15 years of age or older and at least 2 months (greater than or equal to 55 days) post-transplantation (FDA, 2008).

The test assesses the expression of 20 genes, about half of which are directly involved in rejection while the remainder provide other information needed for rejection risk assessment. It is hoped the results of this test will decrease the number of necessary EMBs. Among the proposed benefits are the AlloMap test's ability to differentiate mild rejection, for which histologic findings may be the least accurate, and the potential for monitoring physiologic responses to steroid weaning. It has been recognized that the test is not effective at monitoring rejection within the first 6 months of transplantation, and it is yet unclear what a high AlloMap score might mean in the setting of no histologic rejection.

These patterns of gene expression, detected in peripheral blood by the AlloMap testing, were studied in the Cardiac Allograft Rejection Gene Expression Observation Study (CARGO), which included eight U.S. cardiac transplant centers where 650 heart transplant recipients were tested. Results of the CARGO study have appeared in abstracts presented at the 2005 annual meeting of the International Society of Heart and Lung Transplantation. While the results were promising, the data was considered inadequate to permit firm scientific conclusions regarding how use of this test will impact the management of heart transplant recipients (Deng, 2006). There have been subsequent validation studies and sub-study analyses of the CARGO results which provided additional data regarding the potential utility of the AlloMap test in detecting transplant rejection (Bernstein, 2007; Mehra, 2007b; Mehra, 2008).

Results of another trial were published in 2010. The Invasive Monitoring Attenuation through Gene Expression (IMAGE) trial , which was sponsored by the manufacturer of AlloMap (XDx,

Inc.), was a randomized, event-driven, noninferiority trial which was conducted at 13 U.S. transplant centers between January 2005 and October 2009 (with median follow-up of 19 months). This trial included 602 selected transplant recipients who had undergone a transplant more than 6 months prior and who were considered at low risk for rejection. The purpose of this study was to compare rejection outcomes between those who underwent routine EMB and those who were monitored with the AlloMap gene expression profiling test. The primary outcome was the first occurrence of rejection with hemodynamic compromise, graft dysfunction due to other causes, death, or retransplantation. Results indicated that a strategy of monitoring for rejection that involved gene-expression profiling, as compared with routine biopsies, was not associated with an increased risk of serious adverse outcomes and resulted in the performance of significantly fewer biopsies. During the median follow-up period (19 months), subjects who were monitored with AlloMap and those who underwent routine EMB had similar 2 year cumulative rates of the composite primary outcome (14.5% and 15.3%, respectively; hazard ratio with gene-expression profiling, 1.04; 95% confidence interval, 0.67 to 1.68). The 2 year rates of death from any cause were also similar in the two groups (6.3% and 5.5%, respectively; p=0.82). Although the limited power of the study did not allow for firm conclusions regarding the utility of AlloMap as a substitute for EMB, the authors concluded that gene expression profiling of peripheral blood specimens may offer a reasonable alternative to routine biopsies, for monitoring cardiac transplant rejection, if the interval since transplantation is at least 6 months and the individual is considered to be at low risk for rejection (Pham, 2010).

In 2010, the International Society of Heart and Lung Transplantation (ISHLT) issued guidelines for the care of heart transplant recipients which included the following:

- The standard of care for adult heart transplant recipients is to perform periodic endomyocardial biopsy (EMB) during the first 6-12 months after transplant for rejection surveillance; (Class IIa, Level of Evidence: C)
- After the first year post-transplant, EMB surveillance every 4-6 months is recommended for patients at higher risk of late acute rejection; (Class IIa, Level of Evidence: C)
- Gene expression profiling using the AlloMap test can be used to rule out acute heart rejection (grade 2 or greater) in appropriate low-risk patients between 6 months and 5 years post-transplant (Class IIa, Level of Evidence: B).

The recommendation for AlloMap is based on the results of the CARGO and IMAGE trials (Costanzo, 2010).

In summary, the current ISHLT recommendations for the use of AlloMap in limited clinical protocols, the results of the IMAGE trial, and input from the transplant practice community support the use of AlloMap to assess risk for rejection in clinically stable heart transplant recipients between 1 and 5 years post-transplant.

Background/Overview

Breath Test

Although the current gold standard test for detecting rejection is EMB, this is limited in accuracy, has a high degree of inter-observer variability, and may yield tissue that is not representative of the overall pathology. It is also invasive and can lead to infections, arrhythmias, or ventricular perforation. Despite these limitations, the breath test is currently not established as a substitute for EMB.

***Note:** A Humanitarian Use Device (HUD) is a device that has been given special approval by the FDA under the Humanitarian Device Exemption (HDE) regulations and is utilized in special circumstances where a condition is so rare (fewer than 4000 individuals in the U.S. per year) that testing of large numbers of subjects is not feasible. In these special situations, the FDA may grant an HDE provided that: the device does not pose an unreasonable or significant risk of illness or injury; and the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Additionally, the FDA notes that the applicant must demonstrate that no comparable devices are available to treat or diagnose the disease or condition, and that they could not otherwise bring the device to market. The labeling for an HUD must state that the device is a Humanitarian Use Device and that, although the device is authorized by federal law, the effectiveness of the device for the specific indication has not been demonstrated. (FDA, 2004)

AlloMap Molecular Expression Testing

The California Technology Assessment Forum (CTAF) conducted a technology assessment of gene-expression profiling for the diagnosis of heart transplant rejection in 2006, at which time it

was determined that the use of gene-expression profiling did not meet CTAF criteria when used to manage heart transplant patients. The CTAF assessment stated that:

> Gene expression profiling offers the potential for a non-invasive test that may replace endomyocardial biopsy as the gold standard for transplant rejection. However, given the history of poor reproducibility of other gene expression profiles in the recent past, it is prudent to require independent confirmation of the CARGO study results before widespread adoption of the AlloMap gene expression profile to monitor heart transplant patients for early detection of rejection occurs (CTAF, 2006).

This initial CTAF determination was based on concerns around the post-hoc change in the threshold used to define a positive test result in the CARGO study and the small size of this primary validation study, in addition to the fact that there were no studies, published to date, comparing the clinical outcomes of individuals monitored with gene expression profiling to those monitored with EMB (CTAF, 2006).

In 2010, the CTAF conducted a systematic re-review of available published evidence focusing on results of the AlloMap test which included six observational studies and one randomized trial. Three of the publications included in this review reported on subsets of participants from the CARGO trial, as well as results of the IMAGE trial and concluded that, "This technology meets CTAF's assessment criteria for safety, effectiveness and improvement in health outcomes when used to manage heart transplant patients at least one year post-transplant." The CTAF assessment included the following conclusions:

> The AlloMap gene expression profile has a high negative predictive value, but a low positive predictive value. Thus, it may be useful to avoid biopsy in stable patients, but the high false positive rate precludes its use to definitively diagnose acute cellular rejection. Endomyocardial biopsies will still need to be performed in all patients with elevated AlloMap scores and all patients with clinical signs of rejection. The IMAGE trial provides data supporting the non-inferiority of a monitoring strategy for heart transplant patients incorporating the AlloMap gene expression profile in lieu of routine endomyocardial biopsy. However, the data only support such strategies in patients more than a year post-transplant. More data are needed to confirm the tests utility earlier in the post-transplant period when the majority of endomyocardial biopsies are performed (CTAF/Tice, 2010).

In 2011, the Blue Cross Blue Shield Association published a Technology Assessment Report of gene expression profiling as a noninvasive method to monitor for cardiac allograft rejection. This review and analysis of the available published evidence concluded that the use of gene expression profiling as a noninvasive method to monitor for cardiac allograft rejection does not meet the TEC criteria. The following are some summarized conclusions:

> Although a higher score is associated with a greater likelihood of rejection class 3A or higher, the diagnostic characteristics of AlloMap® testing are uncertain. Study methods are unclear, study samples are incompletely described, numbers of cases of rejection are apparently small, and cutoff scores appear to have been determined post hoc. The sensitivity of the test for detecting rejection is uncertain (TEC, 2011).

Definitions

Allograft rejection: The recipient's immune system rejects the donor heart.

Endomyocardium: The innermost lining of the heart.

Endomyocardial biopsy: A tissue sample of the endomyocardium.

Heart transplant: Removal of a human heart and replacing it with a donor heart.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

CPT
81599

	Unlisted multianalyte assay with algorithmic analysis [when specified as AlloMap test]
86849	Unlisted immunology procedure [when specified as AlloMap test]

ICD-9 Diagnosis ***[For dates of service prior to 10/01/2015]***

V42.1	Organ or tissue replaced by transplant, heart

ICD-10 Diagnosis ***[For dates of service on or after 10/01/2015]***

Z48.21	Encounter for aftercare following heart transplant
Z94.1	Heart transplant status

When services are Investigational and Not Medically Necessary:
For the Allomap test when medically necessary criteria are not met.

When services are also Investigational and Not Medically Necessary:
For the procedure code listed below in all instances, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

0085T	Breath test for heart transplant rejection [Heartsbreath test]

ICD-9 Diagnosis ***[For dates of service prior to 10/01/2015]***
All diagnoses

ICD-10 Diagnosis ***[For dates of service on or after 10/01/2015]***
All diagnoses

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Index

AlloMap
Breath Test as an Aid for Diagnosis of Heart Transplant Rejection
Gene Expression Molecular Profiling
Heartsbreath

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	05/07/2015	Medical Policy & Technology Assessment Committee (MPTAC) review. References were updated.
Reviewed	05/15/2014	MPTAC review. The Rationale and References were updated.
Reviewed	05/09/2013	MPTAC review. References were updated.
Reviewed	05/10/2012	MPTAC review. The Background and References were updated.
Revised	05/19/2011	MPTAC review. The position on AlloMap molecular expression testing has been changed to now consider medically necessary when criteria are met. The Rationale, Background, Coding and Reference sections were updated.
Reviewed	05/13/2010	MPTAC review. The Background and Reference sections were updated.
Reviewed	05/21/2009	MPTAC review. Updated Reference section.
Reviewed	05/15/2008	MPTAC review. References were updated.
	02/21/2008	The phrase "investigational/not medically necessary" was clarified to read "investigational and not medically necessary." This change was approved at the November 29, 2007 MPTAC meeting.
Reviewed	05/17/2007	MPTAC review. Reference section was updated.
Reviewed	06/08/2006	MPTAC review. References were updated and information was added about the CARGO Study of AlloMap testing.
Revised	07/14/2005	MPTAC review. AlloMap® molecular testing added as investigational/not medically necessary.
Revised	04/28/2005	MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organizations	Last Review Date	Document Number	Title
Anthem, Inc			No prior document
WellPoint Health Networks, Inc.	12/02/2004	2.04.32	Breath Test for Use as an Aid in the Diagnosis of Heart Transplant Rejection

Caloric Vestibular Test

CPT Codes:
92537 Caloric vestibular test with recording, bilateral; bithermal (ie, one warm and one cool irrigation in each ear for a total of four irrigations)
92538 monothermal (ie, one irrigation in each ear for a total of two irrigations)

Issue: CPT 92537 and 92538 replace deleted code 92543 (caloric vestibular test) which was Ancillary. When this code was reviewed as a new code in 2004, it was determined that this test was used only to determine brain death, not as a diagnostic test for dizziness or other issues. 92543 was added to the Diagnostic List in 2004, but now appears on the Ancillary List for unclear reasons. A similar test, 92533 (Caloric vestibular test, each irrigation (binaural, bithermal stimulation constitutes 4 tests)) is on lines 297, 422, and 515.

Vestibular tests are generally diagnostic, and are used to evaluate dizziness, vertigo, and imbalance. All tests of the vestibular system (CPT 92531-92548) other than 92543 are on lines 297, 422, and 515. This code series was last reviewed in 2004, and the HSC minutes merely note that these tests were removed from all other lines other than the equivalents to lines 297, 422 and 515. Some of these tests are considered experimental by major insurers, such as computerized dynamic posturography (CPT 92548) which is considered experimental by Aetna (2015).

297 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS
422 MENIERE'S DISEASE
515 VERTIGINOUS SYNDROMES AND OTHER DISORDERS OF VESTIBULAR SYSTEM

HERC staff recommendation:

1) Place **CPT 92537 and 92538** on lines **297** NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS , **422** MENIERE'S DISEASE, and **515** VERTIGINOUS SYNDROMES AND OTHER DISORDERS OF VESTIBULAR SYSTEM
    a. Matches other vestibular test placement.
2) HERC staff to review placement of the entire code series 92531-92548 and bring back to a future meeting
    a. Most are more appropriate for the Diagnostic List
    b. Consider placing 92548 on the Services Recommended for Non-Coverage Table

CPT code	Code description	Current Location	Comments
92531	Spontaneous nystagmus, including gaze	297,422,515	
92532	Positional nystagmus test	297,422,515	
92533	Caloric vestibular test, each irrigation (binaural, bithermal stimulation constitutes 4 tests)	297,422,515	
92534	Optokinetic nystagmus test	297,422,515	
92537	Caloric vestibular test with recording, bilateral; bithermal	NEW	
92538	monothermal	NEW	
92540	Basic vestibular evaluation, includes spontaneous nystagmus test with eccentric gaze fixation nystagmus, with recording, positional nystagmus test, minimum of 4 positions, with recording, optokinetic nystagmus test, bidirectional foveal and peripheral stimulation, with recording, and oscillating tracking test, with recording	297,422,515	
92541	Spontaneous nystagmus test, including gaze and fixation nystagmus, with recording	297,422,515	
92542	Positional nystagmus test, minimum of 4 positions, with recordin	297,422,515	
92543	Caloric vestibular test, each irrigation (binaural, bithermal stimulation constitutes 4 tests), with recording	Ancillary	
92544	Optokinetic nystagmus test, bidirectional, foveal or peripheral stimulation, with recording	297,422,515	
92545	Oscillating tracking test, with recording	297,422,515	
92546	Sinusoidal vertical axis rotational testing	297,422,515	
92547	Use of vertical electrodes	297,422,515	
92548	Computerized dynamic posturography	297,422,515	Considered Experimental

Arterial Pressure Waveform Analysis

CPT code:

93050 Arterial pressure waveform analysis for assessment of central arterial pressures, includes obtaining waveform(s), digitization and application of nonlinear mathematical transformations to determine central arterial pressures and augmentation index, with interpretation and report, upper extremity artery, non-invasive

Issue: Arterial pressure waveform analysis is a relatively new technology, which was previously coded with a temporary category III CPT code, 0311T. This technology is a minimally or non-invasive technique to measure cardiac output, and meant to replace central pulmonary artery catheters. There are several commercial devices which can perform these measurements, such as the PiCCO, VolumeView/EV1000, LiDCOplus, FloTrac/Vigileo, ProAQT/Pulsioflex, and LiDCOrapid. These devices are normally used in the hospital setting and therefore are bundled into the hospital DRG payment. However, there may be some use in the outpatient setting, particularly in surgical centers.

Evidence

1) **Monnet and Teboul 2015**, review
    a. Concluded that "the low invasiveness of such systems…seems to be counterbalanced by a reliability that is lower than for more invasive devices. This lower reliability applies particularly in comparisons of calibrated and uncalibrated pulse contour analyzing devices. Technological improvement in these recently developed devices may reduce this limitation of less invasive devices."
2) **Slagt 2014**, systematic review http://bja.oxfordjournals.org/content/early/2014/01/27/bja.aet429.full.pdf (Not included in packet due to length)
    a. N=65 manuscripts, including 2234 patients
    b. The accuracy and precision of the FloTrac/VigileoTM system can be regarded as sufficient for routine clinical use in hypo- or normodynamic conditions in the absence of large changes in vascular tone
    c. The performance of the system in hyperdynamic conditions, even with the latest software version, is still inadequate
    d. Authors note that the systematic review is limited by the heterogeneity of the included studies, so that conclusions should be drawn cautiously

HERC staff recommendation:

1) Add 93050 (Arterial pressure waveform analysis for assessment of central arterial pressures, includes obtaining waveform(s), digitization and application of nonlinear mathematical transformations to determine central arterial pressures and augmentation index, with interpretation and report, upper extremity artery, non-invasive) to the **Services Recommended for Non-Coverage Table**
    a. Experimental

Minimally Invasive Monitoring

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KEYWORDS

• Hemodynamic monitoring • Cardiac output • Arterial pressure
• Pulse contour analysis • Vascular resistance • Thermodilution

KEY POINTS

- The main advantage of pulse contour analysis is to provide a continuous real-time estimation of cardiac output.
- Calibrated pulse contour analysis devices provide a reliable estimation of cardiac output but are invasive and require frequent recalibrations.
- The reliability of devices using uncalibrated pulse contour analysis is low when vascular resistance changes to a large extent. These devices are more suitable for the perioperative setting than for intensive care units.
- Pulse contour analysis of noninvasive tracings of arterial pressure still needs to be improved.

INTRODUCTION

For many years, the measurement of cardiac output in operating rooms and intensive care units could be performed only with the pulmonary artery catheter. The popularity of the pulmonary artery catheter has progressively declined and some alternative techniques have been developed during recent years,[1] mainly because catheters are invasive, cumbersome to set up, and some of the variables it provides can be difficult to measure and interpret appropriately. Among the alternative techniques, arterial pressure waveform analysis infers cardiac output from the systemic arterial pressure curve. Some of these arterial pressure waveform analysis devices only need an arterial catheter for this purpose and can be considered as minimally invasive. Pulse contour analysis was recently developed for arterial curves that are recorded in a noninvasive way.

Conflicts of interest: Professors X. Monnet and J-L. Teboul are members of the medical advisory board of Pulsion Medical Systems.

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This article first summarizes the technological principles of pulse contour analysis. In particular, it explains how devices differ in whether or not they need to be calibrated. The literature on the reliability of arterial pressure waveform analysis for estimating cardiac output is reviewed. In addition, the role of such devices with respect to the other hemodynamic monitoring devices is discussed.

PRINCIPLES OF ARTERIAL PRESSURE WAVEFORM ANALYSIS

Two types of device that use arterial pressure waveform analysis have been developed. Some of them (PiCCO by Pulsion Medical Systems, Munich, Germany; LiDCOplus by LiDCO, London, United Kingdom; and VolumeView/EV1000 by Edwards Lifesciences, Irvine, CA) calibrate the pressure waveform analysis with an independent measurement of cardiac output done by transpulmonary dilution. Some other devices (FloTrac/Vigileo by Edwards Lifesciences; LiDCOrapid by LiDCO; MostCare by Vytech Health, Padova, Italy; and ProAQT/Pulsioflex by Pulsion Medical Systems) do not require any calibration for pressure waveform analysis and are minimally invasive because they only require a standard arterial catheter.

This article briefly describes the functioning principle of both kinds of pressure waveform analysis device. However, the precise algorithms used by the devices are not disclosed by the manufacturers.

Calibrated Devices

These devices integrate 2 independent techniques for measuring cardiac output: arterial pressure waveform analysis and transpulmonary dilution (with cold saline for PiCCO and VolumeView/EV1000, and with lithium for LiDCOplus).

PiCCO and VolumeView/EV1000

Principles common to both devices The PiCCO and VolumeView/EV1000 devices use a pressure waveform analysis that is based on the principle that stroke volume is proportional to arterial pulse pressure and inversely proportional to arterial compliance. In the early 1990s, Wesseling and colleagues[2] computed the aortic flow from the systemic arterial pressure in humans. They simulated a 3-element model including the characteristic impedance of the aorta, the arterial compliance, and systemic vascular resistance (**Fig. 1**). They described for the first time that it is possible to monitor cardiac output continuously from pulse contour analysis.[2]

Based on this principle, all devices estimating cardiac output from pressure waveform analysis record the arterial pressure curve from a peripheral artery and automatically compute cardiac output from it. Overall, for most devices, the analysis is supported by 4 principles:

1. The amplitude of the pressure curve of the aorta is proportional to stroke volume and to a multiplication factor k.
2. k is inversely proportional to the arterial compliance.
3. The arterial pressure at the periphery is different from the arterial pressure at the aortic level (see **Fig. 1**). This difference is called the pulse wave amplification phenomenon. Because of the reduction of arterial diameter from the aorta to the periphery, the amplitude of the arterial pressure signal increases along the arterial tree.
4. The amplification of pulse along the arterial tree depends on the arterial resistance.

As a result, arterial pressure waveform analysis devices must:

1. Analyze the geometry of the arterial pressure curve signal
2. Estimate the arterial compliance

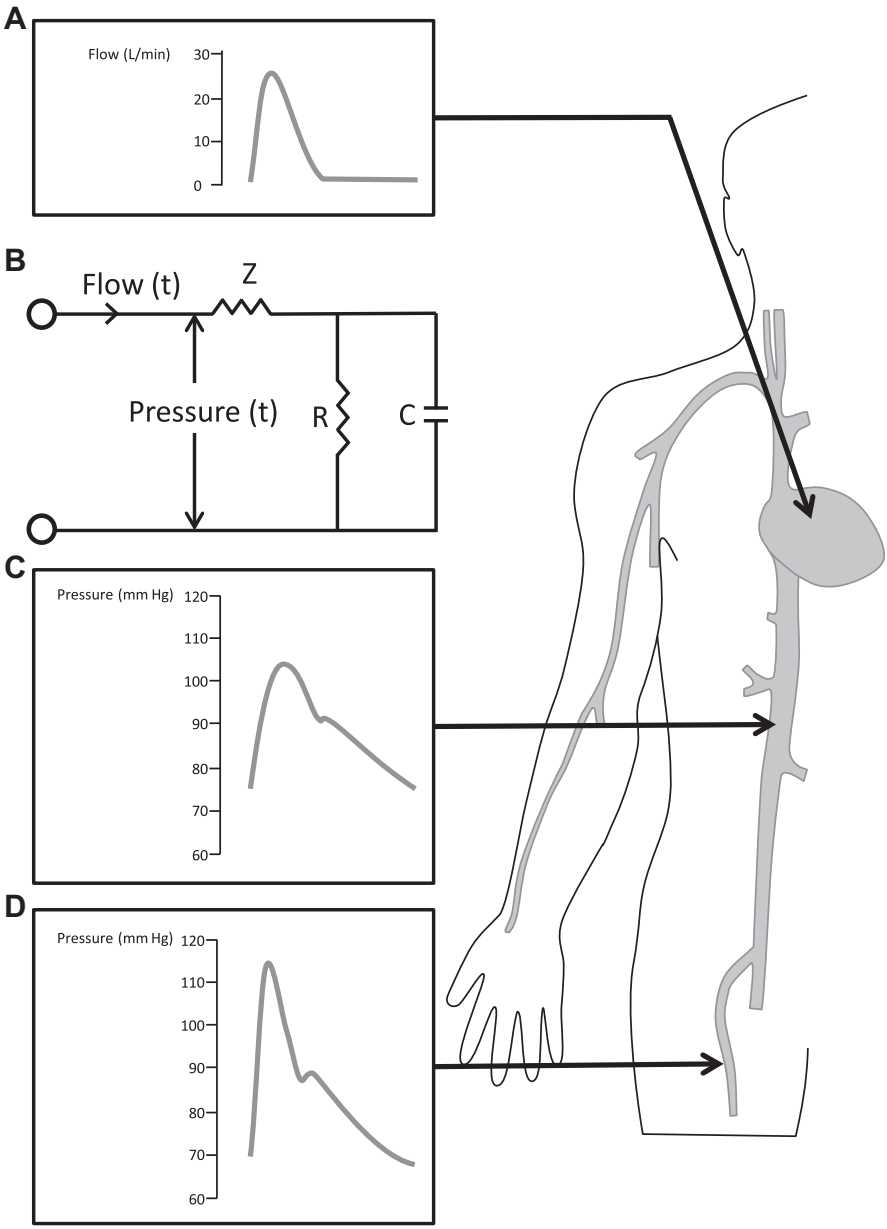


Fig. 1. Pulse pressure analysis. The flow ejected out of the left ventricle (*A*) generates a pressure at the aortic level (*C*) and at the femoral level (*D*). The relationship between flow and the aortic pressure can be represented in a 3-element model (*B*), according to Wesseling.[2] In this model, Z is the characteristic impedance of the aorta, t is time, R is the total arterial resistance, and C is the total compliance of the arterial system.

3. Estimate the aortic pressure from a peripheral arterial pressure
4. Take into account the level of arterial tone

PiCCO With this device, pulse contour analysis estimates cardiac output by integrating the area under the systolic part of the arterial curve and dividing it by the aortic compliance.[3] In addition to the area under the systolic part of the curve, the system takes into account some geometric properties of the pressure curve, such as the time of the dicrotic notch. The arterial compliance is estimated by a proprietary algorithm when calibration is performed (ie, at each time cardiac output is measured by transpulmonary thermodilution). In addition, the algorithm takes into account the systemic vascular resistance, which is continuously tracked by another proprietary algorithm.

Resistance is estimated by dividing mean arterial pressure by the value of cardiac output obtained by transpulmonary thermodilution.

Calibrating the PiCCO pulse contour analysis by transpulmonary thermodilution is justified because the latter technique provides an estimation of cardiac output that is reliable[4] and precise[5] compared with classic pulmonary thermodilution. Moreover, transpulmonary thermodilution has the advantage of providing many other variables besides cardiac output, such as extravascular lung water,[6] pulmonary vascular permeability, the cardiac function index (a marker of the cardiac systolic function),[7] and the global end-diastolic volume (a marker of cardiac preload).[4] All these additional variables may be helpful in the decision-making process of hemodynamic resuscitation.

Between 2 calibrations, compliance and resistance are constantly reassessed by an algorithm that mainly takes into account the arterial pressure curve and the first derivative of pressure on time according to the equation:

$$SV = Cal \times \int \text{systole}\,[P(t)/SVR + C(p) \times dp/dt] \times dt$$

where *SV* is stroke volume; *Cal* is calibrating factor; *P(t)* is arterial pressure; *SVR* is systemic vascular resistance; and *C(p)* is arterial compliance, which is calculated from arterial pressure.

With this constant reassessment of the arterial compliance, the system tends to adapt its estimation of cardiac output to the modifications of the hemodynamic status between 2 calibrations by transpulmonary thermodilution.

Because it requires transpulmonary thermodilution and because transpulmonary thermodilution requires a central venous catheter and a large-diameter femoral arterial catheter, the PiCCO device must be considered more as less invasive than as minimally invasive.[8]

Another disadvantage of the PiCCO device is that it requires frequent recalibrations. A study found that the estimation of cardiac output by pulse contour analysis became insufficiently reliable if the previous calibration was performed more than 1 hour before.[9] The drift of pulse contour analysis–derived cardiac output is particularly important if arterial resistance changes to a large extent. In practice, this does not mean that the pulse contour analysis should be systematically recalibrated every hour in every patient, but rather that, in case of hemodynamic instability, calibration should be performed if it has not been performed for more than 1 hour.

Volumeview/EV1000 The VolumeView/EV1000 device is another transpulmonary thermodilution device that, in many aspects, works like the PiCCO, at least as far as can be ascertained from the manufacturer. Like the PiCCO, the system uses transpulmonary thermodilution to calibrate the pulse contour analysis–derived estimation of

cardiac output. The estimation of cardiac output is based on the algorithm that is also used by the FloTrac/Vigileo device (discussed later). As with the PiCCO device, because of the arterial catheter required by transpulmonary thermodilution, the VolumeView/EV1000 is less invasive rather than minimally invasive.

LiDCOplus

The LiDCOplus calibrates pressure waveform analysis by lithium transpulmonary dilution. With this technique, lithium chloride is injected as an intravenous bolus into a central vein, and its concentration in arterial blood is then measured over time by a lithium-sensitive electrode attached to a peripheral arterial catheter. Lithium dilution has been shown to be reliable compared with the pulmonary artery catheter[10,11] and to be precise.[12]

The arterial pressure waveform analysis with the LiDCOplus, which uses the PulseCO algorithm, is the same as for the LiDCOrapid device and is detailed later. Note that the use of lithium is not authorized in all countries.

Uncalibrated Devices

All these devices share the advantage of not requiring calibration by thermodilution. The technique they use for pressure waveform analysis differs slightly between devices.

FloTrac/Vigileo

With this system, stroke volume is estimated as:

$$SV = K \times \text{pulsatility}$$

where *K* is a constant that quantifies arterial resistance and compliance.

K is estimated from the morphometric data of the patient and is based on the method described by Langewouters and colleagues[13] and supported by a large database of pressure tracings recorded in hyperdynamic and vasoplegic patients.[14] The estimation is based on K and the arterial pulsatility. The device provides the starting value of K. Then, K is automatically adapted every 60 seconds by taking into account some geometric properties of the arterial pressure curve, such as skewness and kurtosis. Pulsatility is estimated from the standard deviations of pulse pressure.

In practice, the device consists of a standard arterial catheter and a standard arterial line that is connected to a disposable specific pressure transducer (FloTrac). The pressure transducer is connected to the Vigileo device, which performs analysis and displays cardiac output.

ProAQT/Pulsioflex

Like the FloTrac/Vigileo system, the more recent ProAQT/Pulsioflex does not need any external calibration of pressure waveform analysis. Nevertheless, the main distinction of this device is that the initial value of cardiac output from which the pulse contour analysis is started is not estimated by pulse contour analysis but by an innovative proprietary algorithm that performs an autocalibration. It uses the biometric values (age, height, and weight) as well as mean arterial pressure and heart rate. The cardiac output value is inferred from a statistical analysis of these data; this analysis is confidential and is not a Windkessel model. After the initial estimation of cardiac output, the ProAQT/Pulsioflex performs pulse contour analysis with a method similar to that of the PiCCO.

With the ProAQT/Pulsioflex, an automatic autocalibration of cardiac output can also be done at any time by just clicking a button. This autocalibration is supposed to

reduce the drift that may have occurred since the previous estimation. In addition, it is also possible to manually enter a value for cardiac output measured by another technique (eg, echocardiography). The pulse contour analysis then starts from this external calibration value.

In practice, the device works with a standard arterial catheter and arterial line, which are connected to a specific disposable pressure transducer (ProAQT), which is connected to the monitor (Pulsioflex).

LiDCOrapid

This device is an evolution of the LiDCOplus that does not require any calibration. Pressure waveform analysis uses the same PulseCO algorithm as the LiDCOplus (described earlier). The PulseCO algorithm is based on the principles of conservation of mass and power and is not based on a Windkessel approach. Stroke volume is calculated from an analysis of the stroke volume–induced pulsatile change in the pressure waveform.

In addition, the arterial compliance is inferred from the age, height, and weight of the patient through established nomograms. The system does not need any calibration but, as with the ProAQT/Pulsioflex, it is possible to manually enter a value of cardiac output measured by an independent technique.

Pressure recording analytical method

The pressure recording analytical method (PRAM) is embedded in the MostCare device. With this method, the arterial pressure waveform analysis is based on the complex theory of perturbations. The estimation of cardiac output is grossly based on the area under the arterial pressure curve, on the analytical description of the arterial pressure waveform, and on the instantaneous acceleration of the arterial vessel cross-sectional area.

With this technique, the arterial impedance is only estimated by the characteristics of the arterial pressure curve, with no need for any calibration and independently from the morphometric data of the patient.[15]

RELIABILITY OF ARTERIAL PRESSURE WAVEFORM ANALYSIS DEVICES

The validation of devices providing a pressure-based estimation of cardiac output has been the purpose of several studies. It is difficult to summarize them, because they have provided heterogeneous results. Moreover, the technique used as the reference (eg, the pulmonary artery catheter) has its own limitations. An example of this is shown in **Fig. 2**, which is adapted from a study in which the pulmonary artery catheter showed bias and limits of agreement that were similar to those of some pulse waveform analysis devices (see **Fig. 2**).[16] Nevertheless, this article aims to clarify the validation of different devices.

Calibrated Devices

PiCCO

The validation of the pulse contour analysis of the PiCCO device has been performed by some clinical studies comparing it with the pulmonary artery catheter, which was used as a reference. Overall, these studies show that this reliability is acceptable.[3,9,17–23] Note that, as stated earlier, the closer the measurement from a previous calibration, the better the reliability.[9]

The validation of a device measuring cardiac output should be based not only on its accuracy, which is its ability to provide a value that is close to the true value, but also on its precision, which is the ability to provide values that are close to each other. In

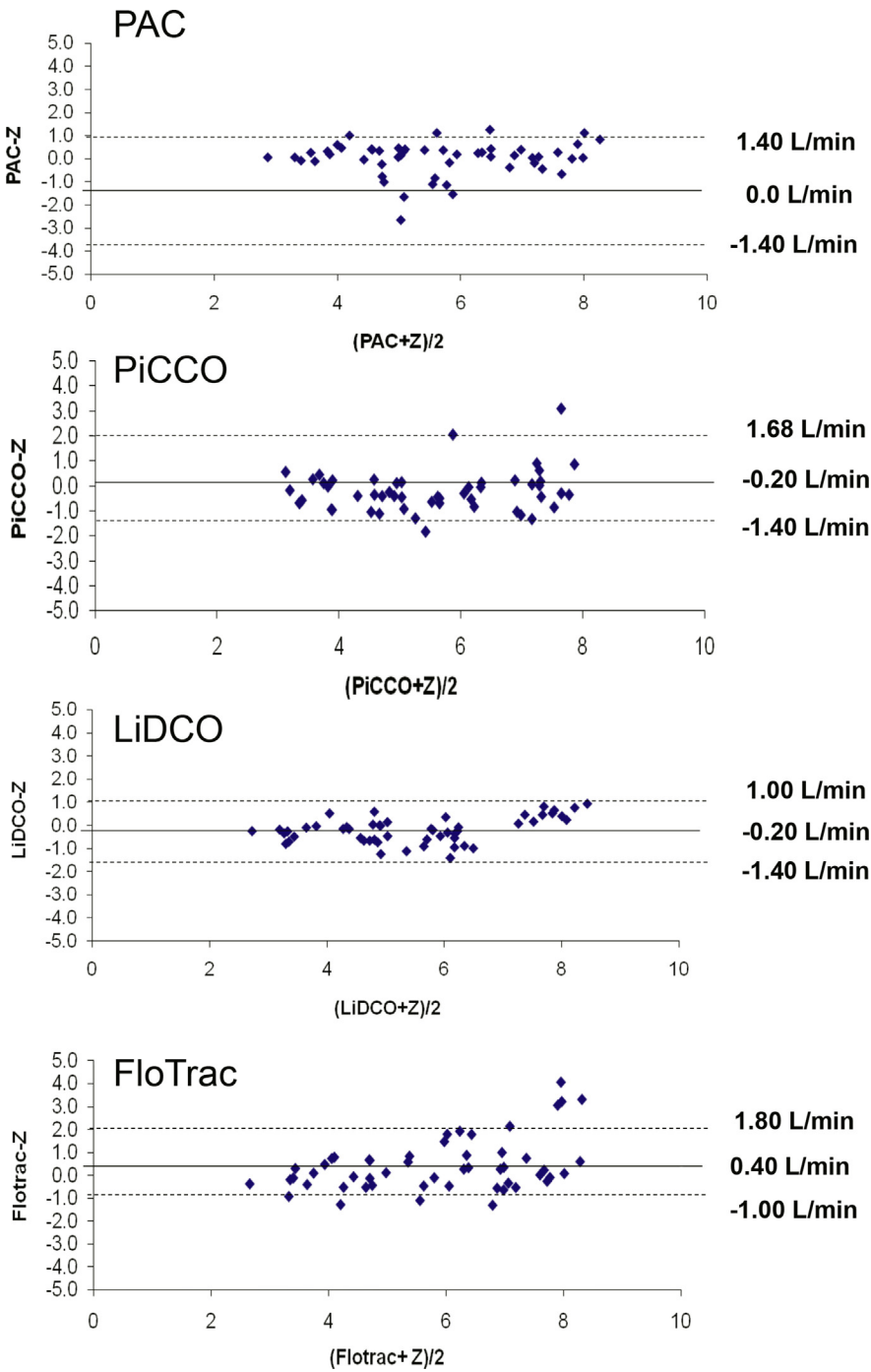


Fig. 2. Bland-Altman analysis of each device against the mean of all devices across all patients, wherein pulmonary arterial catheter (PAC), thermodilution cardiac output, and continuous cardiac output measured by the PAC are pooled to be 1 variable (*Z*-statistic). Solid line, mean difference (bias); dotted line, limits of agreement (bias $\pm$ 1.96 standard deviation). (*From* Hadian M, Kim HK, Severyn DA, et al. Cross-comparison of cardiac output trending accuracy of LiDCO, PiCCO, FloTrac and pulmonary artery catheters. Crit Care 2010;14:R212.)

this regard, the coefficient of variation of pulse contour analysis with the PiCCO is less than 2%,[9] which means that, if the patient's condition is stable, even small changes in cardiac output detected by pulse contour analysis should be considered as reliable.[24]

LiDCOplus

Reliability of the LiDCOplus device compared with thermodilution methods has been reported by concordant studies.[25–27] Because of its specific PulseCO algorithm, the estimation of cardiac output by the LiDCOplus is supposed to be less sensitive to changes in the morphology of the arterial curve than pulse contour analysis, especially in cases of vasopressor administration. The technique is also supposed to be less sensitive to arterial line damping than other pulse wave analysis techniques. Nevertheless, these potential advantages have not been shown until now.

Volumeview/EV1000

The reliability of pulse contour analysis measured by the more recent VolumeView/EV1000 has so far been shown by only 1 study,[28] which also reported a good tracking ability compared with transpulmonary thermodilution.

Overall, it is reasonable to consider that the calibrated pulse contour analysis systems are reliable to estimate cardiac output. This reliability is mostly related to the possibility to regularly reset the estimation with transpulmonary dilution, a technique that itself provides a reliable measurement of cardiac output. These calibrated devices have the disadvantage of requiring injections of cold boluses or lithium. With the PiCCO and VolumeView/EV1000 devices, such injections require a large-diameter arterial catheter, so these techniques cannot be described as minimally invasive.

Uncalibrated Devices

FloTrac/Vigileo

Results concerning the reliability of the uncalibrated devices are not as concordant as for the calibrated devices. The FloTrac/Vigileo, as the precursor of such devices, was the most studied. Although some studies reported good reliability,[14,29–34] some others found opposite results.[35–47]

One possible explanation for this discrepancy may concern the setting in which the studies were conducted. Overall, most of the studies showing good reliability of the FloTrac/Vigileo were conducted in perioperative settings,[29–31,33] even though poor results were also obtained in such patients.[48] The poorest results were obtained in critically ill patients[40,41,43,47] or patients undergoing liver surgery[36–39,44–46] (ie, in patients with large changes in vasomotor tone). The reliability of the FloTrac/Vigileo seems to decrease if the vasomotor tone changes to a large extent.[35,38,41–43] Note that the reliability of a cardiac output monitoring device depends not only on its ability to provide a reliable absolute value of cardiac output but also on its ability to track changes in cardiac output.

For instance, Monnet and colleagues[43] found that the reliability of the last version of the FloTrac/Vigileo was much poorer in tracking the changes in cardiac output when they were induced by changing the dose of norepinephrine than by administering a volume expansion. It was similarly reported that the reliability of the FloTrac/Vigileo was poor during liver transplant surgery and that the poorest results were obtained when the systemic vascular resistance changed to a large extent.[38] In some patients before surgical intervention, the FloTrac/Vigileo provided a good estimation of cardiac output compared with esophageal Doppler when preload was increased, whereas it was poor when the arterial tone was modified by ephedrine or phenylephrine.[42] The trending ability of the third version of the FloTrac/Vigileo during phenylephrine administration similarly was the lowest when the systemic vascular resistance was the

highest.[49] Overall, the failure of uncalibrated pulse contour analysis may be related mainly to its inability to take into account changes in vascular tone.

All situations in which the arterial pressure waveform is abnormally modified are also at risk for unreliability of uncalibrated pulse contour analysis. This unreliability can arise in cases of dampening of the arterial pressure curve, which justifies careful checking of the arterial line when such devices are used. This unreliability can be related to air bubbles, blood clots in the arterial catheter, or kinking of the arterial catheter line.

Aortic valvular regurgitation[35] and stenosis[50] are other conditions in which pulse contour analysis by the FloTrac/Vigileo has been shown to have poor reliability, even though it could still reliably track the changes in cardiac output.[50] Such uncalibrated devices produced conflicting results with intra-aortic balloon pumps, some with acceptable[51] and others with unacceptable biases and limits of agreement.[35]

The reliability of the uncalibrated devices may also depend on the arterial site to which they are connected. Nevertheless, some results showed no[41,52] or minimal[53] differences between cardiac output values obtained from the femoral and the radial sites.

LiDCOrapid

The LiDCOrapid device has had less evaluation. In patients undergoing cardiac surgery, the estimation of cardiac output by pulse power analysis was influenced by the mean arterial pressure, yielding an unacceptable bias.[54] A high percentage error was also recently reported for this device compared with esophageal Doppler monitoring, associated with a bad trending ability.[55]

ProAQT/Pulsioflex

The recent ProAQT/Pulsioflex device still requires validation studies. In particular, these studies should investigate whether the autocalibration allowed by the ProAQT/Pulsioflex improves the measurement of cardiac output.

Pressure recording analytical method

The PRAM algorithm of the MostCare device has been investigated by only a few studies. In patients after cardiac surgery and with an intra-aortic balloon pump, this uncalibrated estimation of cardiac output was acceptable.[15] In septic patients receiving norepinephrine, and compared with the pulmonary artery catheter, the PRAM system showed an acceptable percentage of error.[56] This finding was also shown in cardiac surgical patients; even in those with an intra-aortic balloon pump[51,57,58] (ie, patients in whom pulse waveform analysis is usually considered inoperative). In contrast with these positive results, another study from a different group found a profound lack of agreement between PRAM and the pulmonary artery catheter, without any obvious explanation for this discrepancy.[59]

THE ADVANTAGE OF A REAL-TIME MONITORING OF CARDIAC OUTPUT WITH ARTERIAL PRESSURE WAVEFORM ANALYSIS

The most important advantage of the arterial pressure waveform contour analysis technique is that it provides a real-time measurement of cardiac output because it is based on a measurement of stroke volume from beat to beat. This real-time measurement is useful in 2 ways.

Stroke Volume Variation

All the arterial pressure waveform analysis devices measure the percentage of variation of stroke volume over time. This variation within the respiratory cycle is associated

with preload reserve, based on the same principle as pulse pressure variation.[60] Even though stroke volume and pulse pressure variations are not exactly the same,[61,62] stroke volume variation has regularly been shown to predict fluid responsiveness as reliably as pulse pressure variation.[63–80]

Note that stroke volume variation has the same limitations as pulse pressure variation.[81] It cannot be used to predict fluid responsiveness in cases of spontaneous breathing activity, cardiac arrhythmias, low tidal volume and low lung compliance,[82] and open chest conditions.

Short-term Changes in Cardiac Output

Arterial pressure waveform analysis is particularly suitable for assessing changes in cardiac output occurring on a very short time scale. Note that this is not the case for the semicontinuous thermodilution by the pulmonary artery catheter, which reflects only the changes in cardiac output that occurred during the last few minutes.

For instance, arterial pressure waveform analysis is particularly suitable for assessing the effects of the passive leg raising test[24,63,64,82–84] or of the end-expiratory occlusion test,[24,82,85] which exert their hemodynamic effects on periods of time that are too short to use a dilution method.

CONTEXT OF USE OF ARTERIAL PRESSURE WAVEFORM ANALYSIS DEVICES

Uncalibrated Devices

The typical indication for the uncalibrated pulse contour analysis devices is the monitoring of surgical interventions in high-risk surgical patients. First, as detailed earlier, it is in this context that the reliability of cardiac output measurement by such devices has been found to be the best. The low invasiveness of the uncalibrated devices is particularly appropriate for these patients with a low risk of complications during surgery.

The poor results obtained during liver surgery[36–39,44–46] suggest that the uncalibrated devices should not be used during this type of surgery, which is associated with large changes in vascular tone. Also, during cardiac surgery, hemodynamic evaluation by uncalibrated pulse contour analysis devices is likely to be too limited. In addition, the measurement of cardiac output, along with stroke volume variation, fits the requirement of hemodynamic monitoring during surgery, which is to alert the anesthesiologist of a hemodynamic impairment.[86]

In surgery for high-risk patients, hemodynamic monitoring by uncalibrated devices attached to a therapeutic protocol has been found to decrease the risk of complications, either with the PiCCO[87] or the Vigileo.[88,89] This finding reinforces the message that a preemptive hemodynamic intervention improves the postoperative outcome of such patients.[90]

Calibrated Devices

These devices are likely more indicated in critically ill patients. In these patients, who often receive vasopressors and in whom the vasomotor tone is unstable, external calibration reduces the errors in cardiac output measurement by pulse contour analysis related to changes in vasomotor tone. The invasiveness of such devices is more acceptable in critically ill patients than in surgical patients because of the greater severity of their illnesses, even though the rate complications related to the calibrated pulse contour analysis devices is low.[8] In addition, in this context the intensivist may be interested in the other hemodynamic variables that pulmonary thermodilution provides besides pulse contour analysis.[91]

PULSE CONTOUR ANALYSIS FROM A NONINVASIVE ARTERIAL PRESSURE CURVE

The Nexfin device (Edwards Lifesciences, Irvine, CA) provides a noninvasive estimation of the arterial pressure curve and uses it to compute cardiac output.

Tracing of the Noninvasive Arterial Curve

The Nexfin device allows a continuous estimation of the arterial pressure curve through the volume-clamp method.[92] For this purpose, the device includes an inflatable cuff that is wrapped around a finger. It also includes a photoplethysmographic device that measures the diameter of the finger arteries. At each systole, the photoplethysmographic device senses the increase of the finger arteries' diameters. A fast servo-controlled system immediately inflates the cuff in order to keep the arteries' diameters constant. Therefore, cuff pressure reflects the arterial pressure. Its continuous measurement allows estimation of the arterial pressure curve.

This measurement of arterial pressure by Nexfin has been largely validated for measuring arterial pressure.[93–100]

Estimation of Cardiac Output

To estimate cardiac output, the device uses a pulse contour waveform analysis. With this device, aortic impedance is determined from a 3-element Windkessel model that incorporates the influence of nonlinear effects of arterial pressure and of the patient's age, height, weight, and gender on aortic mechanical properties.[101] The Nexfin method was developed on a database including invasive and noninvasive arterial pressures together with thermodilution cardiac output values.

The reliability of this estimation of cardiac output has provided discrepant results, with both positive[94,102–108] and negative studies.[100,109,110]

The most plausible hypothesis explaining this discrepancy is the difference in the population of interest. The studies that showed a better reliability of the Nexfin were conducted in the operating theater,[102,103] in patients having cardiac surgery after discontinuation of mechanical ventilation and inotropes,[94] in patients undergoing resynchronization therapy,[105] in an echocardiography laboratory,[104] or in healthy subjects.[107] By contrast, the studies reporting unreliability of the technique[100,109] included critically ill patients, most with septic shock. In such patients, poor finger perfusion likely impedes the correct assessment of the finger pressure curve by the volume-clamp method, which includes an analysis of the finger photoplethysmographic signal. This limitation suggests that such a device is more suitable for the operating theater than for intensive care units.

SUMMARY

The number of less invasive devices monitoring cardiac output using a pressure-based estimation of cardiac output has increased during recent years. The low invasiveness of such systems, which is a particular advantage in operating theaters, seems to be counterbalanced by a reliability that is lower than for more invasive devices. This lower reliability applies particularly in comparisons of calibrated and uncalibrated pulse contour analyzing devices. Technological improvement in these recently developed devices may reduce this limitation of less invasive devices.

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Photoscreening

CPT code:

99177 Instrument based ocular screening (eg, photoscreening, automated-fractions), bilateral; with onsite analysis

Issue: Photoscreening is a method to screen for vision issues in young or non-verbal/non-cooperative children.

The USPSTF (2011) recommends vision screening for all children at least once between the ages of 3 and 5 years, to detect the presence of amblyopia or its risk factors (grade B recommendation). The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of vision screening for children <3 years of age (I statement).

Similar code 99174 (Instrument-based ocular screening (eg, photoscreening, automated-refraction), bilateral) is currently on the Services Recommended for Non-Coverage Table.

From the American Association for Pediatric Ophthalmology and Strabismus:

> Photoscreening is a form of pediatric vision screening that uses a special-purpose camera to determine how well a child can see. It is an alternative to visual acuity-based screening with an eye chart. By detecting special light reflexes from each eye the devices produce images that can help identify refractive errors (like a prescription for glasses) and ocular misalignments (strabismus). When present, these conditions place a child at risk for amblyopia (lazy eye). The camera images can be interpreted by a trained test administrator or by software incorporated into the equipment. If the images show a condition that may lead to amblyopia, a referral should be made by the person performing the photoscreening to a pediatric ophthalmologist for further evaluation. Photoscreening is particularly useful with pre-verbal children (under age 3 yrs), young children (age 3-5 yrs) and older, non-cooperative or non-verbal children. As such, photoscreening offers an alternative to traditional visual acuity screening, providing earlier detection of potential vision problems than has been possible with traditional testing. However, photoscreening cannot determine exactly how well a child's visual acuity is developing. Visual acuity screening thus remains an important component of a child's preventive health care and should still be done when a child is sufficiently mature to respond to this testing (usually age 4-6 years).

Evidence

1) **Chou 2011**, review for USPSTF http://pediatrics.aappublications.org/content/pediatrics/127/2/e442.full.pdf (Not included in packet due to length)
    a. Results: Direct evidence on the effectiveness of preschool vision screening for improving visual acuity or other clinical outcomes remains limited and does not adequately address whether screening is more effective than no screening. Regarding indirect evidence, a number of screening tests have utility for identification of preschool-aged children with vision problems.

   i. In 8 studies of the Medical Technology and Innovations (MTI) photoscreener, the median positive likelihood ratio (PLR) was 6.2 (range: 2.4– 8.7) and the median negative likelihood ratio (NLR) was 0.26 (range: 0.06–0.67).
   ii. From 2 studies of the iScreen photoscreener, a median PLR of 7.3 (range: 6.2– 8.6) and median NLR of 0.25 (range: 0.09–0.67) were reported.
   iii. Two studies of the Visiscreen 100 photoscreener resulted in a median PLR of 7.0 (range: 3.5–14) and median NLR of 0.14 (range: 0.12– 0.16).
b. Conclusions: Although treatments for amblyopia or unilateral refractive error can improve vision in preschool-aged children and screening tests have utility for identifying vision problems, additional studies are needed to better understand the effects of screening compared with no screening.

2) **AHRQ 2004**, systematic review http://www.ahrq.gov/downloads/pub/prevent/pdfser/visualser.pdf (Not included due to length)
   a. Few data are available regarding the performance of screening tests in the primary care practice setting.

Specialty society statements

1) **American Academy of Pediatrics; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus; and American Association of Certified Orthoptists 2012 http://pediatrics.aappublications.org/content/130/5/983** (not included in packet due to length)
   a. Photoscreening and handheld autorefraction may be electively performed in children 6 months to 3 years of age, allowing earlier detection of conditions that may lead to amblyopia, as well as in older children who are unable or unwilling to cooperate with routine acuity screening.
   b. Photoscreening and handheld autorefraction are recommended as an alternative to visual acuity screening with vision charts from 3 through 5 years of age, after which visual acuity screening with vision charts becomes more efficient and less costly in the medical home. Adequate payment for instrument based vision-screening services must be ensured if there is to be widespread adoption of this recommendation.
   c. Alternatively, the use of vision charts and standard physical examination techniques to assess amblyopia in children 3 to 5 years of age in the medical home remains a viable practice at the present time.
   d. There is no recommendation for mass screening at this time.
   e. Regardless of the type of photoscreening system used, the evaluator must know how to properly apply the technology and understand the limitations of the test, such as the possible occurrence of false-positive and false-negative results as they apply to the population being tested.
   f. Advocates for additional research of photoscreening and handheld autorefraction devices and other vision screening methods to elucidate the validity of results, efficacy, cost-effectiveness, and payment policies for

identifying amblyogenic factors in different age groups and subgroups of children.

Summary:
Early vision screening is recommended by major evidence based organizations; however, clinical exam and standard eye chart testing appears to be sufficient. Photoscreening and similar technology needs to be further studied before widespread implementation.

HERC staff recommendation:

1) Add 99177 (Instrument based ocular screening (eg, photoscreening, automated-fractions),bilateral; with onsite analysis) to the **Services Recommended for Non-Coverage Table**
    a. Consistent with current code placement and evidence

Vision Screening for Children 1 to 5 Years of Age: US Preventive Services Task Force Recommendation Statement

WHAT'S KNOWN ON THIS SUBJECT: In 2004, the US Preventive Services Task Force (USPSTF) provided a statement about screening for visual impairment among children <5 years of age.

WHAT THIS STUDY ADDS: The 2004 USPSTF recommendation statement is updated here.

abstract

FREE

OBJECTIVE: The goal was to provide an update of the 2004 US Preventive Services Task Force (USPSTF) statement about screening for visual impairment in children <5 years of age.

METHODS: The USPSTF examined evidence on the association of screening for visual impairment in children 1 to 5 years of age with improved health outcomes, the accuracy of risk factor assessment and screening tests, the effectiveness of early detection and treatment, and the harms of screening and treatment.

RECOMMENDATION: The USPSTF recommends vision screening for all children at least once between the ages of 3 and 5 years, to detect the presence of amblyopia or its risk factors (grade B recommendation). The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of vision screening for children <3 years of age (I statement). *Pediatrics* 2011;127:340–346

AUTHOR: US Preventive Services Task Force

KEY WORDS

vision screening, preventive services, children

ABBREVIATION

USPSTF—US Preventive Services Task Force

The USPSTF makes recommendations about preventive care services for patients without recognized signs or symptoms of the target condition. It bases its recommendations on a systematic review of the evidence of the benefits and harms and an assessment of the net benefit of the service.

The USPSTF recognizes that clinical or policy decisions involve more considerations than this body of evidence alone. Clinicians and policy makers should understand the evidence but individualize decision-making to the specific patient or situation.

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VISION SCREENING IN CHILDREN AGES 1 TO 5 YEARS: CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

Population	Children ages 3 to 5 years	Children younger than 3 years of age
Recommendation	Provide vision screening Grade: B	No recommendation Grade: I (Insufficient Evidence)

Screening tests	Various screening tests are used in primary care to identify visual impairment in children, including: • Visual acuity test • Stereoacuity test • Cover-uncover test • Hirschberg light reflex test • Autorefraction • Photoscreening
Timing of screening	No evidence was found regarding appropriate screening intervals.
Interventions	Primary treatment for amblyopia includes the use of corrective lenses, patching, or atropine therapy of the non-affected eye. Treatment may also consist of a combination of interventions.
Balance of harms and benefits	There is adequate evidence that early treatment of amblyopia in children ages 3 to 5 years leads to improved visual outcomes. There is limited evidence on harms of screening, including psychosocial effects, in children ages 3 years and older. There is inadequate evidence that early treatment of amblyopia in children younger than 3 years of age leads to improved visual outcomes.
Suggestions for Practice Regarding the I Statement	In deciding whether to refer children younger than 3 years of age for screening, clinicians should consider: • *Potential preventable burden:* screening later in the preschool years seems to be as effective as screening earlier • *Costs:* initial high costs associated with autorefractors and photoscreeners • *Current practice:* typical vision screening includes assessment of visual acuity, strabismus, and stereoacuity; children with positive findings should be referred for a comprehensive ophthalmologist exam

For a summary of the evidence systematically reviewed in making these recommendations, the full recommendation statement, and supporting documents please go to www.uspreventiveservicestaskforce.org.

FIGURE 1
Clinical summary of USPSTF recommendation for vision screening in children 1 to 5 years of age. For a summary of the evidence systematically reviewed in making these recommendations, the full recommendation statement, and supporting documents please go to www.uspreventiveservicestaskforce.org.

SUMMARY OF RECOMMENDATIONS AND EVIDENCE

The USPSTF recommends vision screening for all children at least once between the ages of 3 and 5 years, to detect the presence of amblyopia or its risk factors. This recommendation is a grade B recommendation.

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of vision screening for children <3 years of age. This statement is an I statement.

See Figure 1 for a summary of the recommendations and suggestions for clinical practice, Table 1 for a description of the USPSTF grades, and Table 2 for a description of the USPSTF classification of levels of certainty about net benefit.

RATIONALE

Importance

Approximately 2% to 4% of preschool-aged children have amblyopia, an alteration in the visual neural pathway in the developing brain that can lead to permanent vision loss in the affected eye. Amblyopia usually occurs unilaterally but can occur bilaterally. Identification of vision impairment before school entry could help identify children who may benefit from early interventions to correct or to improve vision.

Detection

The USPSTF found adequate evidence that vision screening tools have reasonable accuracy in detecting visual impairment, including refractive errors, strabismus, and amblyopia.

Benefits of Detection and Early Intervention

The USPSTF found adequate evidence that early treatment for amblyopia, including the use of cycloplegic agents, patching, and eyeglasses, for children

TABLE 1 USPSTF Grade Definitions and Suggestions for Practice

Grade	Grade Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer/provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer/provide this service.
C	The USPSTF recommends against routinely providing the service. There may be considerations that support providing the service for an individual patient. There is moderate or high certainty that the net benefit is small.	Offer/provide this service only if there are other considerations in support of offering/providing the service for an individual patient.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage use of this service.
I	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	See the clinical considerations in the USPSTF recommendation statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

TABLE 2 USPSTF Levels of Certainty Regarding Net Benefit

Level of Certainty	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies with representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by factors such as (1) the number, size, or quality of individual studies; (2) inconsistency of findings across individual studies; (3) limited generalizability of findings to routine primary care practice; or (4) lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect might change, and this change might be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess the effects on health outcomes. Evidence is insufficient because of (1) limited number or size of studies; (2) important flaws in the study design or methods; (3) inconsistency of findings across individual studies; (4) gaps in the chain of evidence; (4) lack of generalizability of findings to routine primary care practice; or (5) lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.

The USPSTF defines certainty as the "likelihood that the USPSTF assessment of the net benefit of a preventive service is correct." The net benefit is defined as benefits minus harms of the preventive service, as implemented for a general, primary care population. The USPSTF assigns a certainty level on the basis of the nature of the overall evidence available for assessment of the net benefit of a preventive service.

3 to 5 years of age leads to improved visual outcomes. The USPSTF found inadequate evidence that early treatment of amblyopia for children <3 years of age leads to improved visual outcomes.

Harms of Detection and Early Intervention

The USPSTF found limited evidence regarding harms of screening, including psychosocial effects, for children ≥3 years of age. False-positive screening results may lead to the overprescribing of corrective lenses. Adequate evidence suggests that the harms of treatment of amblyopia for children ≥3 years of age are limited to reversible loss of visual acuity resulting from patching of the nonaffected eye. The USPSTF found inadequate evidence of the harms of screening and treatment for children <3 years of age.

USPSTF Assessment

The USPSTF concludes with moderate certainty that vision screening for children 3 to 5 years of age has a moderate net benefit. The USPSTF concludes that the benefits of vision screening for children <3 years of age are uncertain and that the balance of benefits and harms cannot be determined for this age group.

CLINICAL CONSIDERATIONS

Patient Population Under Consideration

This recommendation applies to all children 1 to 5 years of age.

Screening Tests

Various screening tests that are feasible in primary care are used to identify visual impairment among children. These tests include visual acuity tests, stereoacuity tests, the cover-uncover test, and the Hirschberg light reflex test (for ocular alignment/strabismus), as well as the use of autorefractors (automated optical instruments that detect refractive errors) and photoscreeners (instruments that detect amblyogenic risk factors and refractive errors).

Treatment

Primary treatment for amblyopia includes the use of corrective lenses, patching, or atropine treatment of the nonaffected eye. Treatment

may consist of a combination of interventions.

Suggestions for Practice Regarding I Statement

In deciding whether to refer children <3 years of age for screening, clinicians should consider the following.

Potential Preventable Burden

Most studies show that screening and treatment later in the preschool years seem to be as effective at preventing amblyopia as screening and treatment earlier in life.

Costs

Potential disadvantages of using photoscreeners and autorefractors are the initial high costs associated with the instruments and the need for external interpretation of screening results with some photoscreeners.

Current Practice

Typical components of vision screening include assessments of visual acuity, strabismus, and stereoacuity. Younger children often are unable to cooperate with some of the screening tests performed in clinical practice, such as visual acuity testing. Steroacuity testing often is omitted and may be performed incorrectly when attempted. Screening of younger children may be difficult and often yields false-positive results because of the child's inability to cooperate with testing. Children with positive findings should be referred for a full ophthalmologic examination, to confirm the presence of vision problems, and further treatment.

Screening Intervals

The USPSTF did not find adequate evidence to determine the optimal screening interval.

OTHER CONSIDERATIONS

Research Needs and Gaps

Several gaps in the evidence were identified. All treatment trials in the literature review enrolled children ≥3 years of age. Well-designed studies are needed to identify the optimal age for initiation of screening, optimal screening methods, and optimal screening frequency. Longitudinal studies that link optimal screening tests to the identification of children with visual impairments are needed. Additional studies are needed to determine the most-favorable combinations of screening tests, as well as the optimal treatment for amblyopia and the optimal treatment duration. There also is a need for studies that examine the long-term benefits and harms of preschool vision screening, such as quality of life, school performance, and labeling or anxiety.

DISCUSSION

Burden of Disease

The most common causes of vision impairment in children are amblyopia and associated risk factors (strabismus, anisometropia, astigmatism, and hyperopia) and refractive errors not associated with amblyopia (Table 3). Amblyopia is a disorder characterized by abnormal processing of visual images by the brain during a critical period of vision development, which results in a permanent reduction in visual acuity. It is associated with conditions that interfere with normal binocular vision, such as strabismus (ocular misalignment), anisometropia (a large difference in refractive power between the 2 eyes), cataracts (lens opacity), ptosis (eyelid drooping), and other structural impairments. Amblyopia is regarded as a disease of childhood; however, its effects are irreversible if left untreated, and it is the most common cause of monocular vision loss among adults 20 to 70 years of age. An important risk of amblyopia is that an unrelated, severe vision impairment or blindness might occur in the nonaffected eye, resulting in severe vision loss or even legal blindness.

Scope of Review

The review on which this recommendation is based examined evidence regarding the following topics: the association of screening for visual impairment among children 1 to 5 years of age with improved health outcomes, the accuracy of risk factor assessment, the accuracy of screening tests, the effectiveness of early detection, the effectiveness of treatment, and the harms of screening and treatment.

Accuracy of Screening Tests

No studies evaluated the accuracy or reliability of risk factor assessment in preschool vision screening. There also was no evidence on the outcomes of targeted versus universal preschool vision screening.

Twenty-six studies, including 3 of poor quality and 23 of fair quality, evaluated

TABLE 3 Risk Factors for Amblyopia

Condition	Description
Amblyopia	Functional reduction in visual acuity characterized by abnormal processing of visual images, which is established by the brain during a critical period of vision development
Strabismus	Ocular misalignment; most common cause of amblyopia
Anisometropia	Asymmetric refractive error between the 2 eyes, which causes image suppression in the eye with the larger error.
Astigmatism	Blurred vision at any distance because of abnormal curvature of the cornea or lens
Hyperopia	Farsightedness; visual images come to focus behind the retina

the diagnostic accuracy of various preschool vision screening tests.[1,2] However, none of the tests was associated consistently with both high sensitivity and high specificity (ie, >90%) for specific amblyogenic risk factors. Cycloplegic refraction testing was included in the reference standard examination in 21 studies. Vision screening tests included tests of visual acuity, stereoacuity, and ocular alignment, as well as tests using autorefractors and photoscreeners. The largest study comparing screening tests was the Vision in Preschoolers study,[3,4] which compared 10 different screening tests. In the Vision in Preschoolers study, the Random Dot E stereoacuity test (StereoOptical Co, Chicago, IL), the Randot Stereo Smile Test II (StereoOptical Co, Chicago, IL), and the iScreen (iScreen, Inc, Memphis, TN) and Medical Technologies, Inc photoscreeners (Riviera Beach, FL) were associated with lower sensitivity (at a similar specificity), compared with the Lea symbols test (Precision Vision, Inc, LaSalle, IL), the HOTV visual acuity test (Precision Vision, Inc, LaSalle, IL), and the Retinomax (Nikon, Inc, Melville, NY) and Power Refractor II (Plusoptix, Nuromberg, Germany) autorefractors; however, differences in likelihood ratio estimates were relatively small. The cover-uncover test was associated with lower sensitivity and higher specificity, compared with the other tests. The available studies on vision screening that evaluated various tests in various combinations found that combinations of tests were generally associated with greater diagnostic accuracy, compared with single tests of visual acuity, stereoacuity, or ocular alignment, although there is insufficient evidence to recommend a specific combination of tests.[1]

Vision screening requires a cooperative child, and this factor is influenced by the age of the child. Nine fair-quality studies evaluated screening tests for vision impairment in stratified age groups.[1] Most of the evidence was limited and inconsistent. Four studies found no definitive differences according to age, because testability generally exceeded 80% to 90% for children 3 years of age, with small increases through 5 years of age. Four studies found that testability rates were lower for most screening tests (Random Dot E test, Lea symbols test, and SureSight autorefractor [Welch Allyn, Inc, Skaneateles Falls, NY]) for children 1 to 3 years of age, compared with children 3 to 5 years of age. One large, statewide screening study of the Medical Technologies photoscreener found 94% testability by 1 year of age.[1]

Effectiveness of Early Detection and Treatment

There were no randomized controlled trials that compared preschool vision screening with no screening. All studies evaluated reported on vision outcomes for children ≥3 years of age. There were no studies available that evaluated school performance or other functional outcomes in screened versus unscreened populations.

One fair-quality, nested, randomized trial found that periodic screening from the ages of 8 months to 37 months was associated with a 1% decrease in the prevalence of amblyopia at age 7.5 years, compared with one-time screening at 37 months of age.[5] However, the difference was statistically significant for only 1 definition of amblyopia. A limitation of the study was that it was not possible to separate effects of earlier screening from those of repeated screening.

Three fair- or good-quality trials with older preschool-aged children (3–5 years of age) with mild/moderate amblyopia or unilateral refractive errors (with or without amblyopia) reported that treatment (patching and/or eyeglasses) resulted in a statistically significant but small (<1 line on the Snellen eye chart) average improvement in visual acuity in the affected eye, compared with no treatment, after follow-up periods of 5 weeks to 1 year.[6–8] Benefits were greater for children with more-severe visual impairment at baseline. One trial found that, in a subgroup of children with more-severe visual impairment at baseline, patching was associated with visual acuity improvement of 1 to 2 lines on the Snellen eye chart, compared with no treatment.[6] Five fair- or good-quality trials found no differences in visual acuity improvement in the affected eye between shorter and longer daily patching regimens,[9,10] among different atropine treatment regimens,[11,12] or between patching and atropine treatment.[13]

Potential Harms of Screening and Treatment

Potential harms of preschool vision screening include psychosocial effects such as labeling and anxiety, unnecessary referrals because of false-positive screening results, and unnecessary use of corrective lenses or treatments to prevent amblyopia, which can have potential effects on long-term vision or function. The USPSTF found limited evidence regarding the harms of vision screening for children <5 years of age. However, the data that are available suggest that harms do exist. Six of 7 studies reported false-positive rates of >70% in low-prevalence populations.[1] One large study of a statewide, preschool photoscreening program found that 20% of children who did not meet criteria for amblyogenic risk factors were prescribed eyeglasses; however, there is no evidence available on the long-term effects of unnecessary corrective lenses or treatment for amblyopia.[14]

Five fair-quality trials with children ≥3 years of age demonstrated that some amblyopia treatments are associated with an increased risk of reversible, short-term loss of visual acuity in the nonaffected eye.[1] Although 1 short-term (5-week) trial found no increased risk of visual acuity loss in the nonaffected eye associated with patching versus no patching, another trial found that patching of the nonaffected eye was associated with an increased risk of visual acuity loss of ≥2 lines on the Snellen eye chart, compared with atropine treatment (9% vs 1.4%; $P < .001$). One trial found that atropine treatment plus a plano lens was associated with an increased risk of visual acuity loss of ≥1 line, compared with atropine treatment alone (17% vs 4%; $P = .005$). In both trials that found deficits, visual acuity in the nonaffected eye returned to baseline levels for most children. Two other trials found no difference in the risk of visual acuity loss in the nonaffected eye in direct comparisons of different patching or atropine treatment regimens.[1]

Evidence on adverse psychosocial effects of amblyopia treatments is limited. Two randomized controlled trials examined adverse psychosocial effects and found that children were more likely to be upset about patching and eyeglasses, compared with eyeglasses alone, and that patching was associated with worse emotional well-being than atropine treatment.[1] In a cohort study, screening and treatment did not increase the incidence of bullying but unexpectedly decreased the odds of bullying by ~50% for children offered screening, compared with those not offered screening, perhaps because the screened children completed patching regimens at an earlier age.[2]

Estimate of Magnitude of Net Benefit

The USPSTF found adequate evidence that treatment for amblyopia or unilateral refractive errors is associated with moderate improvements in visual acuity for children 3 to 5 years of age and, in theory, permanent improvements throughout life. Although the average improvement in visual acuity resulting from treatment for amblyopia was ~1 line on a Snellen eye chart, the USPSTF concluded that the benefits are moderate because untreated amblyopia results in permanent, uncorrectable vision loss and the potential benefits are experienced over the individual's life span. Harms from treatment seem to be minimal. Therefore, the USPSTF concluded with moderate certainty that the overall net benefit is moderate.

How Does Evidence Fit With Biological Understanding?

Amblyopia is a functional reduction in visual acuity characterized by abnormal processing of visual images by the brain. The loss in visual acuity is not immediately reversible with simple refractive correction, and it is unlikely to resolve spontaneously if left untreated. Amblyopia typically becomes irreversible if the child is not treated by 6 to 10 years of age. Therefore, preschool screening seems to be consistent with the current biological understanding of amblyopia and the importance of detecting it during a critical period in development.

Response to Public Comments

A draft version of this recommendation statement was posted for public comment on the USPSTF Web site from October 5 through October 23, 2009. A small number of comments were received from individuals or organizations. All comments were reviewed in the creation of this final recommendation.

UPDATE OF PREVIOUS USPSTF RECOMMENDATION

This recommendation updates the 2004 recommendation, in which the USPSTF recommended vision screening for all children <5 years of age.[15] The USPSTF now recommends vision screening for the presence of amblyopia and its risk factors for all children 3 to 5 years of age (B recommendation). For children <3 years of age, the USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of vision screening (I statement).

RECOMMENDATIONS OF OTHERS

Preschool vision screening is recommended by several other organizations; however, the specific age for initiation of screening and the particular screening tests that are recommended vary. The American Academy of Family Physicians is updating its recommendation, which is similar to that of the USPSTF.[16] The American Academy of Pediatrics recommends screening for distance visual acuity, ocular alignment, and ocular media clarity for children 3 to 6 years of age and older.[17] The American Academy of Ophthalmology and the American Association for Pediatric Ophthalmology and Strabismus recommend vision screening during the preschool years.[18] The American Optometric Association recommends a comprehensive eye examination at 3 years of age.[19]

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Committee on Practice and Ambulatory Medicine and Section on Ophthalmology

Use of Photoscreening for Children's Vision Screening

ABSTRACT. This statement asserts that all children should be screened for risk factors associated with amblyopia. Guidelines are suggested for the use of photoscreening as a technique for the detection of amblyopia and strabismus in children of various age groups. The American Academy of Pediatrics favors additional research of the efficacy and cost-effectiveness of photoscreening as a vision screening tool.

ABBREVIATION. AAP, American Academy of Pediatrics.

INTRODUCTION

The goal of all vision screening is to detect poor vision or risk factors that interfere with vision and normal visual development. It is accepted that early diagnosis and treatment yield better visual outcomes. The prevalence of amblyopia is estimated to be 1% to 4% in children[1]; however, only 21% of preschool-aged children and even fewer younger children are screened for this condition.[2,3] In the policy statement "Eye Examination and Vision Screening in Infants, Children, and Young Adults," the American Academy of Pediatrics (AAP) recommends that all newborns and children be screened for such risk factors regularly.[4] The components of the vision screening vary by age. Despite the availability of many screening options, many children permanently lose vision each year as a result of amblyopia, media opacities, and treatable ocular disease processes.

VISION SCREENING

Performing vision screening in the pediatric population involves many difficulties. Infants and young preverbal children are unable to provide subjective responses to visual acuity testing and do not easily cooperate with testing of ocular alignment or stereoacuity. It also is difficult to screen certain older children, such as those who are nonverbal or have developmental delays. Targeted populations, particularly those in medically underserved areas, may be difficult to reach. Screening approaches must be simple and generally successful to enhance the likelihood of their use.

Other challenges involved with vision screening include false-positive and false-negative results caused by low sensitivity and specificity of certain tests. Evaluators may vary in their ability to administer and interpret test results. Regardless of the system or approach used, it is unacceptable to fail to identify children at risk of preventable vision loss or treatable visual disability because of failure to screen or because of false-negative test results.

PHOTOSCREENING

Photoscreening is a vision screening technique used to screen for amblyogenic factors, such as strabismus, media opacities, and significant refractive errors, in 1 or both eyes in children.[5,6] Photoscreening has the potential to increase the currently low screening rates. Using a camera or video system appropriately equipped for photoscreening, images of the pupillary reflexes (reflections) and red reflexes (Brückner test) are obtained.[7] Other than having to fixate on the appropriate target long enough for the photoscreening, little cooperation is needed from the child. Data are then analyzed by the evaluator, reviewing center, or computer for amblyogenic factors, and positive findings are noted. Children who do not pass the test may be referred for a complete eye examination.

As a technique to screen for amblyogenic risk factors, photoscreening appears to offer certain conveniences and advantages over traditional methods of vision screening, especially in its availability to screen children who are the most difficult to screen but in whom the prevalence of amblyopia is higher than in the general pediatric population. This includes children at high risk for eye problems, such as premature infants or children with developmental delays or a family history of eye problems.

Photoscreening does not represent a single technique or piece of equipment. Different optical systems can be used for photoscreening. Interpretation of screened images may be performed onsite or offsite in a reading center or with an automated system.

Each photoscreening system may have its own advantages and disadvantages, and it appears that results published in the literature for one system are not necessarily valid for others. Studies performed by different investigators using the same photoscreening apparatus may yield a wide range of results in sensitivity, specificity, and predictive values when onsite interpretation is required.[8–15] Likewise, it is not certain that data gathered about different groups of children or different settings can be extrapolated to other groups or settings.

In general, it is difficult to compare efficacies of various vision screening methods, such as stereoacuity testing, autorefraction, red reflex testing, and cover testing, and then determine if photoscreening has better positive and negative predictive values.

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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This is attributable in part to lack of uniformity in pass-fail criteria for significant refractive errors.

More research is needed to establish how photoscreening can be best used. Photoscreening offers hope in improving vision screening rates in infants, preverbal children, and those with developmental delays who are the most difficult to screen. Photoscreening has not been shown to be superior to other vision screening tests currently used to screen 4- to 5-year-olds. In older children, currently available vision screening techniques can be used reliably.

RECOMMENDATIONS

1. Vision screening should be performed at the earliest possible age and at regular intervals during childhood as recommended by the AAP. The goal remains to eliminate preventable blindness and treatable visual disability.
2. Photoscreening is an innovative tool that can facilitate vision screening in children, especially in children who are difficult to screen (ie, infants, toddlers, and children with developmental delays). Photoscreening systems are one option to increase the screening rate in preschool-aged children.
3. Regardless of the type of photoscreening system used, the evaluator must know how to properly apply the technology and understand the limitations of the test, such as the possible occurrence of false-positive and false-negative results as they apply to the population being tested.
4. Photoscreening needs to be studied more extensively. The AAP favors additional research of photoscreening devices and other vision screening methods in large, controlled studies to elucidate validity of results, efficacy, and cost-effectiveness for identifying amblyogenic factors in different age groups as well as subgroups of children. The goal remains to eliminate preventable childhood blindness and treatable visual disability.

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Use of Photoscreening for Children's Vision Screening

Committee on Practice and Ambulatory Medicine and Section on Ophthalmology

Pediatrics 2002;109;524

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/109/3/524.full.html

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Code	Description	Placement	Comments
G0296	Counseling visit to discuss need for lung cancer screening (ldct) using low dose ct scan (service is for eligibility determination and shared decision making)	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS	See low dose CT scan summary
G0297	Low dose ct scan (ldct) for lung cancer screening	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS	See low dose CT scan summary
G0298	Hiv antigen/antibody, combination assay, screening	Services Recommended for Non-Coverage	HIV antibody test uses one of a couple of valid CPT codes and is what is generally used for screening
G0475	Hiv antigen/antibody, combination assay, screening	Services Recommended for Non-Coverage	See above

For more information on low-dose CT Scan CMS Medicare Decision memo, see:
https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=274

HCPCS codes:
G0296 Counseling visit to discuss need for lung cancer screening (ldct) using low dose ct scan (service is for eligibility determination and shared decision making)
G0297 Low dose ct scan (ldct) for lung cancer screening

Issue: CMS issued a coverage memo (not included in packet due to length) in 2015 which allowed coverage of yearly low dose CT scans for lung cancer screening in a select population (asymptomatic current or recent smokers aged 55-74 with a 30+ pack year smoking history). As part of this memo, CMS required a shared decision making visit, which must be documented in the patient chart. The new HCPCS code is meant to allow reimbursement for such a visit. This visit is only required prior to the first CT scan; subsequent scans can be ordered during routine visits.

> **CMS 2015**
> *For the initial LDCT lung cancer screening service:* a beneficiary must receive a written order for LDCT lung cancer screening during a lung cancer screening counseling and shared decision making visit, furnished by a physician…or qualified non-physician practitioner…A lung cancer screening counseling and shared decision making visit includes the following elements (and is appropriately documented in the beneficiary's medical records):
> 1) Determination of beneficiary eligibility including age, absence of signs or symptoms of lung cancer, a specific calculation of cigarette smoking pack-years; and if a former smoker, the number of years since quitting;
> 2) Shared decision making, including the use of one or more decision aids, to include benefits and harms of screening, follow-up diagnostic testing, over-diagnosis, false positive rate, and total radiation exposure;
> 3) Counseling on the importance of adherence to annual lung cancer LDCT screening, impact of comorbidities and ability or willingness to undergo diagnosis and treatment;
> 4) Counseling on the importance of maintaining cigarette smoking abstinence if former smoker; or the importance of smoking cessation if current smoker and, if appropriate, furnishing of information about tobacco cessation interventions; and
> 5) If appropriate, the furnishing of a written order for lung cancer screening with LDCT

Other information: low dose CT for lung cancer screening in this select population is a USPSTF B recommendation. The current HCPCS code for the CT scan (S8032) is on line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS, as is the ICD-10 code used for screening (Z12.2 Encounter for screening for malignant neoplasm of respiratory organs). Of note, a new HCPCS code (G0297 Low dose ct scan (ldct) for lung cancer screening) has been published with the 2016 HCPCS codes, but the former code S8032 is still a valid code. Both appear to have payment levels associated with them by CMS. Per Encoder Pro, S8032 is not open for payment by Medicare.

HERC staff recommendations:

1) Place G0296 (Counseling visit to discuss need for lung cancer screening (ldct) using low dose ct scan (service is for eligibility determination and shared decision making)) and G0297 (Low dose ct scan (ldct) for lung cancer screening) on line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS

Decision Memo for Screening for Lung Cancer with Low Dose Computed Tomography (LDCT) (CAG-00439N)

Links in PDF documents are not guaranteed to work. To follow a web link, please use the MCD Website.

Decision Summary

The Centers for Medicare & Medicaid Services (CMS) has determined that the evidence is sufficient to add a lung cancer screening counseling and shared decision making visit, and for appropriate beneficiaries, annual screening for lung cancer with low dose computed tomography (LDCT), as an additional preventive service benefit under the Medicare program only if all of the following criteria are met:

Beneficiary eligibility criteria:

- Age 55 – 77 years;
- Asymptomatic (no signs or symptoms of lung cancer);
- Tobacco smoking history of at least 30 pack-years (one pack-year = smoking one pack per day for one year; 1 pack = 20 cigarettes);
- Current smoker or one who has quit smoking within the last 15 years; and
- Receives a written order for LDCT lung cancer screening that meets the following criteria:

- *For the initial LDCT lung cancer screening service:* a beneficiary must receive a written order for LDCT lung cancer screening during a lung cancer screening counseling and shared decision making visit, furnished by a physician (as defined in Section 1861(r)(1) of the Social Security Act) or qualified non-physician practitioner (meaning a physician assistant, nurse practitioner, or clinical nurse specialist as defined in §1861(aa)(5) of the Social Security Act). A lung cancer screening counseling and shared decision making visit includes the following elements (and is appropriately documented in the beneficiary's medical records):
    - Determination of beneficiary eligibility including age, absence of signs or symptoms of lung cancer, a specific calculation of cigarette smoking pack-years; and if a former smoker, the number of years since quitting;
    - Shared decision making, including the use of one or more decision aids, to include benefits and harms of screening, follow-up diagnostic testing, over-diagnosis, false positive rate, and total radiation exposure;
    - Counseling on the importance of adherence to annual lung cancer LDCT screening, impact of comorbidities and ability or willingness to undergo diagnosis and treatment;
    - Counseling on the importance of maintaining cigarette smoking abstinence if former smoker; or the importance of smoking cessation if current smoker and, if appropriate, furnishing of information about tobacco cessation interventions; and
    - If appropriate, the furnishing of a written order for lung cancer screening with LDCT.
- *For subsequent LDCT lung cancer screenings:* the beneficiary must receive a written order for LDCT lung cancer screening, which may be furnished during any appropriate visit with a physician (as defined in Section 1861(r)(1) of the Social Security Act) or qualified non-physician practitioner (meaning a physician assistant, nurse practitioner, or clinical nurse specialist as defined in Section 1861(aa)(5) of the Social Security Act). If a physician or qualified non-physician practitioner elects to provide a lung cancer screening counseling and shared decision making visit for subsequent lung cancer screenings with LDCT, the visit must meet the criteria described above for a counseling and shared decision making visit.
- Written orders for both initial and subsequent LDCT lung cancer screenings must contain the following information, which must also be appropriately documented in the beneficiary's medical records:
    - Beneficiary date of birth;
    - Actual pack - year smoking history (number);
    - Current smoking status, and for former smokers, the number of years since quitting smoking;
    - Statement that the beneficiary is asymptomatic (no signs or symptoms of lung cancer); and
    - National Provider Identifier (NPI) of the ordering practitioner.

Reading radiologist eligibility criteria:

- Board certification or board eligibility with the American Board of Radiology or equivalent organization;
- Documented training in diagnostic radiology and radiation safety;
- Involvement in the supervision and interpretation of at least 300 chest computed tomography acquisitions in the past 3 years;
- Documented participation in continuing medical education in accordance with current American College of Radiology standards; and
- Furnish lung cancer screening with LDCT in a radiology imaging facility that meets the radiology imaging facility eligibility criteria below.

Radiology imaging facility eligibility criteria:

- Performs LDCT with volumetric CT dose index (CTDIvol) of ≤ 3.0 mGy (milligray) for standard size patients (defined to be 5' 7" and approximately 155 pounds) with appropriate reductions in CTDIvol for smaller patients and appropriate increases in CTDIvol for larger patients;
- Utilizes a standardized lung nodule identification, classification and reporting system;
- Makes available smoking cessation interventions for current smokers; and

- Collects and submits data to a CMS-approved registry for each LDCT lung cancer screening performed. The data collected and submitted to a CMS-approved registry must include, at minimum, all of the following elements:

Data Type	***Minimum Required Data Elements***
Facility	Identifier
Radiologist (reading)	National Provider Identifier (NPI)
Patient	Identifier
Ordering Practitioner	National Provider Identifier (NPI)
CT scanner	Manufacturer, Model.
Indication	Lung cancer LDCT screening – absence of signs or symptoms of lung cancer
System	Lung nodule identification, classification and reporting system
Smoking history	Current status (current, former, never). If former smoker, years since quitting. Pack-years as reported by the ordering practitioner. For current smokers, smoking cessation interventions available.
Effective radiation dose	CT Dose Index (CTDIvol).

Data Type	Minimum Required Data Elements
Screening	Screen date Initial screen or subsequent screen

All CMS-approved registries must have the capacity and capability to collect data from any Medicare-eligible imaging facility/department that furnishes lung cancer screening with LDCT, with a catchment area that includes all 50 States, United States Territories, and the District of Columbia. CMS will evaluate each entity interested in participating as a CMS-approved registry to determine if they are capable of meeting the registry and data collection requirements outlined in this national coverage determination, including:

a. Establishment of a steering committee and a governance board for oversight of the registry;
b. Registry management plan, including identification of key personnel;
c. Operational plan and framework that describes mechanisms for collection and submission of data from imaging facilities to the registry;
d. Registry catchment area;
e. Mechanisms for the submission of registry data to CMS electronically;
f. Mechanisms to collect information (e.g.; HICN) in order to permit linkage of registry data with external databases (e.g. Medicare claims data sets);
g. Description of data management and data quality review methods, including validation;
h. Use of CMS-approved standardized data dictionary;
i. Mechanisms for submitting a list of facilities participating in the registry to CMS; and
j. Quality assurance plan.

To apply to function as a CMS-approved registry, interested entities must submit a letter of interest along with detailed supporting information about how the interested entity is able to meet the requirements outlined in this national coverage determination to the following address or via email to caginquiries@cms.hhs.gov.

Centers for Medicare & Medicaid Services
Center for Clinical Standards and Quality
Director, Coverage and Analysis Group
ATTN: Lung Cancer LDCT Screening
Mail Stop: S3-02-01
7500 Security Blvd.
Baltimore, MD 21244

Information regarding CMS-approved registries will be posted on the CMS website.

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TO: Administrative File: CAG-00439N

FROM: Tamara Syrek Jensen, JD
Director, Coverage and Analysis Group

Joseph Chin, MD, MS
Acting Deputy Director, Coverage and Analysis Group
Lead Medical Officer

Lori Ashby
Acting Director, Division of Medical and Surgical Services

Jamie Hermansen, MPP
Lead Health Policy Analyst

Joseph Dolph Hutter, MD, MA
Medical Officer

SUBJECT: Final National Coverage Determination on Screening for Lung Cancer with Low Dose Computed Tomography (LDCT)

DATE: February 5, 2015

I. Decision

The Centers for Medicare & Medicaid Services (CMS) has determined that the evidence is sufficient to add a lung cancer screening counseling and shared decision making visit, and for appropriate beneficiaries, annual screening for lung cancer with low dose computed tomography (LDCT), as an additional preventive service benefit under the Medicare program only if all of the following criteria are met:

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Director, Coverage and Analysis Group
ATTN: Lung Cancer LDCT Screening
Mail Stop: S3-02-01
7500 Security Blvd.
Baltimore, MD 21244

Information regarding CMS-approved registries will be posted on the CMS website.

II. Background

Throughout this document we use numerous acronyms, some of which are not defined as they are presented in direct quotations. Please find below a list of these acronyms and corresponding full terminology.

AAFP – American Academy of Family Physicians
ACR – American College of Radiology
ALA – American Lung Association
AWV – annual wellness visit
CAT – computerized axial tomography
CCI – Charlson comorbidity index
CT – computed tomography
CTDIvol – computed tomography dose index
CXR – chest x-ray
DANTE – Detection and Screening of Early Lung Cancer by Novel Imaging Technology Molecular Assays
DLCST – Danish Lung Cancer Screening Trial
FDA – United States Food and Drug Administration
FDCA – Federal Food, Drug, and Cosmetic Act
JNCCN – Journal of the National Comprehensive Cancer Network
LC – lung cancer
LDCT – low dose computed tomography
MCBS – Medicare Current Beneficiary Survey
mGy – milligray
mSv – millisievert
MILD – Multicentric Italian Lung Detection
NCCN – National Comprehensive Cancer Network
NCI – National Cancer Institute
NCRP – National Council on Radiation Protection and Measurements
NIH – National Institutes of Health
NLST – National Lung Screening Trial
NSCLC – non-small cell lung cancer
PLCO – Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
PMA – premarket approval application
PPV – positive predictive value
RCT – randomized control trial
SEER – Surveillance, Epidemiology, and End Results
USPSTF – United States Preventive Services Task Force

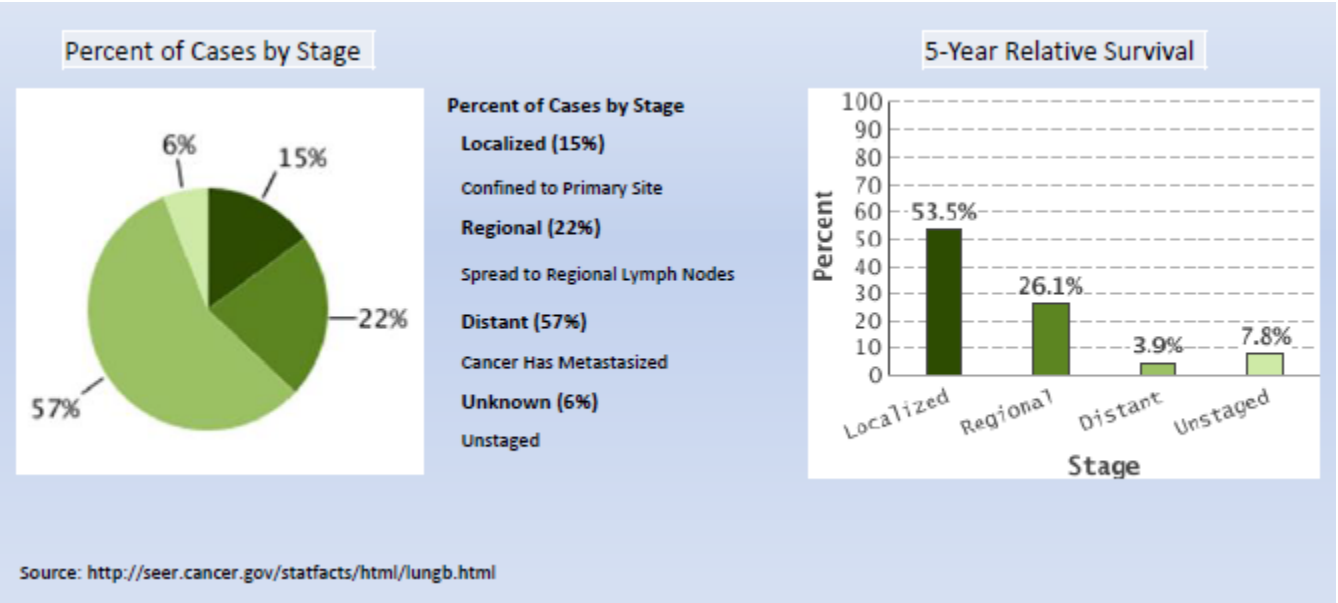
CMS initiated this national coverage determination (NCD) to consider coverage under the Medicare Program for lung cancer screening with low dose computed tomography (LDCT). The scope of our review is limited to the consideration of screening for lung cancer with LDCT. Diagnostic CTs are outside the scope of this national coverage analysis.

Lung cancer (LC) is the third most common cancer and the leading cause of cancer deaths in the United States. It is an important issue for the Medicare population due to the age at diagnosis and at death. In 2013, the National Cancer Institute (NCI) estimated that the number of new cases is over 220,000, with a median age at diagnosis of 70 years. Cancer of the lung and bronchus accounted for over 150,000 deaths in 2013 (more than the total number of deaths from colon, breast and prostate cancer combined) with a median age at death of 72 years.

	Common Types of Cancer	Estimated New Cases 2013	Estimated Deaths 2013
1	Prostate Cancer	238,590	29,720
2	Breast Cancer	232,340	39,620
3	**Lung and Bronchus Cancer**	**228,190**	**159,480**
4	Colon and Rectum Cancer	142,820	50,830
5	Melanoma of the Skin	76,690	9,480
6	Bladder Cancer	72,570	15,210
7	Non-Hodgkin Lymphoma	69,740	19,020
8	Kidney and Renal Pelvis Cancer	65,150	13,680
9	Thyroid Cancer	60,220	1,850
10	Endometrial Cancer	49,560	8,190

Source: http://seer.cancer.gov/statfacts/html/lungb.html

Overall mortality rates for lung and bronchus cancer have decreased only slightly over the past decade. The majority of cases are still diagnosed at a late stage with a low five-year relative survival. (NIH/NCI/SEER 2013).

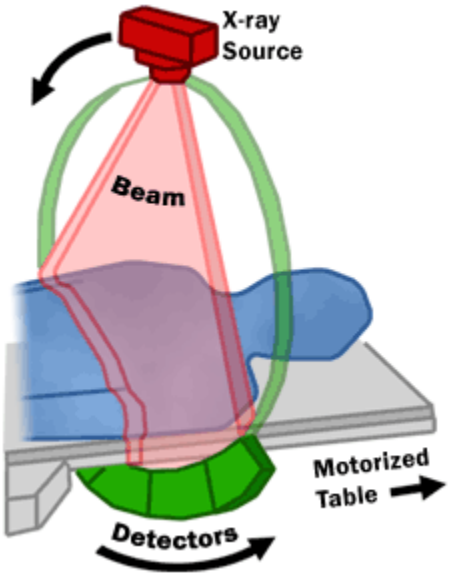


Source: http://seer.cancer.gov/statfacts/html/lungb.html

The National Institutes of Health (NIH) National Cancer Institute (NCI) describes computed tomography (CT) as "an imaging procedure that uses special x-ray equipment to create detailed pictures, or scans, of areas inside the body. It is also called computerized tomography and computerized axial tomography (CAT). Most modern CT machines take continuous pictures in a helical (or spiral) fashion rather than taking a series of pictures of individual slices of the body, as the original CT machines did. Helical CT has several advantages over older CT techniques: it is faster, produces better 3-D pictures of areas inside the body, and may detect small abnormalities better. The newest CT scanners, called multislice CT or multidetector CT scanners, allow more slices to be imaged in a shorter period of time." (NIH/NCI; http://www.cancer.gov/cancertopics/factsheet/Detection/CT)

The United States Food and Drug Administration (FDA) describes the mechanisms of a CT scanner as follows (also see image below): "A motorized table moves the patient through a circular opening in the CT imaging system.

While the patient is inside the opening, an X-ray source and a detector assembly within the system rotate around the patient. A single rotation typically takes a second or less. During rotation, the X-ray source produces a narrow, fan-shaped beam of X-rays that passes through a section of the patient's body. Detectors in rows opposite the X-ray source register the X-rays that pass through the patient's body as a snapshot in the process of creating an image. Many different "snapshots" (at many angles through the patient) are collected during one complete rotation. For each rotation of the X-ray source and detector assembly, the image data are sent to a computer to reconstruct all of the individual "snapshots" into one or multiple cross-sectional images (slices) of the internal organs and tissues."



(US Food and Drug Administration (FDA); http://www.fda.gov/Radiation-EmittingProducts/RadiationEmittingProductsandProcedures/MedicalImaging/MedicalX-Rays/ucm115317.htm)

LDCT is a chest CT scan performed at acquisition settings to minimize radiation exposure compared to a standard chest CT (Smith-Bindman, 2009). Prasad et al. (2002) noted: "[s]everal factors influence patient radiation dose from CT including tube voltage, tube current, scanning time, pitch, slice thickness, and scanning volume. Radiation dose is linearly related to tube current, scanning time, and scan volume and inversely related to pitch. Although scanning times are decreased on modern helical CT scanners, the radiation dose associated with helical scanners is greater than that of other imaging procedures because of the increased tube current and volume of tissue irradiated."

While LDCT reduces radiation exposure, image quality is also reduced which in turn may influence readability. Bankier and Tack (2010) noted: "[t]he concept of reducing the radiation dose in chest CT was first introduced by Naidich et al., (1990) who reduced the tube current on incremental 10-mm collimation CT and showed that with tube current settings as low as 20 mAs, the image quality is sufficient for assessing the lung parenchyma. Although these images were sufficient for diagnostically assessing the lung parenchyma, the increased image noise resulted in marked degradation of the quality of images on mediastinal window settings."

Given the burden of lung cancer on the United States population, a suitable screening test for lung cancer has been sought for many years. The earliest studies were conducted in the 1960's and 1970's, testing sputum

cytology and chest radiography or a combination of both. The initial studies using sputum cytology and/or chest radiography tests failed to conclusively demonstrate improvements in health outcomes, leading the United States Preventive Services Task Force (USPSTF) to give lung cancer screening a grade D recommendation in 1985 and again in 1996 (Humphrey, 2004). Low dose helical computed tomography began being considered for use as a screening modality starting in the 1990's. Naidich et al. (1990) noted: "[a]lthough further evaluation is necessary, the potential of low-dose CT for use in the pediatric population in particular, as well as for screening in patients at high risk for developing lung cancer, is apparent."

With accumulation of evidence on LDCT screening from studies in the late 1990s and early 2000s, the USPSTF updated their recommendation for lung cancer screening to a grade I (insufficient) recommendation and "found there was insufficient evidence to either recommend for or against routinely screening asymptomatic persons for lung cancer with either low-dose computed tomography (LDCT), chest x-ray (CXR), sputum cytology, or a combination of these tests (I statement)" (Humphrey et al., 2013). The USPSTF noted that "screening with LDCT, CXR, or sputum cytology can detect lung cancer at an earlier stage than lung cancer would be detected in an unscreened population; however, the USPSTF found poor evidence that any screening strategy for lung cancer decreases mortality" (USPSTF, 2004). As with many technologies, the initial studies on lung cancer screening with LDCT were observational case-control and cohort studies to generate hypotheses, show feasibility, and to identify the appropriate screening population.

In 2011, the results of the NCI-sponsored National Lung Screening Trial (NLST) were published. The NLST showed that people aged 55 to 74 years with a history of heavy smoking are 20 percent less likely to die from lung cancer if they are screened with low dose helical CT than with standard screening chest x-rays. Previous studies had shown that screening with standard chest x-rays does not reduce the mortality rate from lung cancer. The NLST identified risks as well as benefits. For example, people screened with low dose helical CT had a higher overall rate of false-positive results (that is, findings that appeared to be abnormal even though no cancer was present), leading to a higher rate of invasive procedures (such as bronchoscopy or biopsy), and serious complications from such invasive procedures, than those screened with standard x-rays. (NIH/NCI at http://www.cancer.gov/cancertopics/factsheet/Detection/CT)

In 2014, Moyer and colleagues, on behalf of the USPSTF, released updated recommendations for lung cancer screening: "The USPSTF recommends annual screening for lung cancer with low-dose computed tomography in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery. (B recommendation)" (Moyer for the USPSTF, 2014).

III. History of Medicare Coverage

Pursuant to §1861(ddd) of the Social Security Act, the Secretary may add coverage of "additional preventive services" if certain statutory requirements are met. Our regulations provide:

42 CFR §410.64 Additional preventive services

(a) Medicare Part B pays for additional preventive services not described in paragraph (1) or (3) of the definition of "preventive services" under §410.2, that identify medical conditions or risk factors for individuals if the Secretary determines through the national coverage determination process (as defined in section 1869(f)(1)(B) of the Social Security Act) that these services are all of the following:

(1) Reasonable and necessary for the prevention or early detection of illness or disability.
(2) Recommended with a grade of A or B by the United States Preventive Services Task Force.
(3) Appropriate for individuals entitled to benefits under part A or enrolled under Part B.

(b) In making determinations under paragraph (a) of this section regarding the coverage of a new preventive service, the Secretary may conduct an assessment of the relation between predicted outcomes and the expenditures for such services and may take into account the results of such an assessment in making such national coverage determinations.

A. Current Request

CMS received two formal requests for a national coverage determination (NCD) for lung cancer screening with LDCT, one from Peter B. Bach (Director, Center for Health Policy and Outcomes, Memorial Sloan-Kettering Cancer Center), and another from Laurie Fenton Ambrose (President & CEO, Lung Cancer Alliance). The formal request letters can be viewed via the tracking sheet for this NCA on the CMS website at http://www.cms.gov/medicare-coverage-database/details/nca-tracking-sheet.aspx?NCAId=274.

B. Benefit Category

In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B and must not be otherwise excluded from coverage. Since January 1, 2009, CMS is authorized to cover "additional preventive services" if certain statutory requirements are met as provided under §1861(ddd) of the Social Security Act.

IV. Timeline of Recent Activities

Date	Action
February 10, 2014	

Date	Action
	CMS initiates this national coverage analysis. A 30-day public comment period began.
March 12, 2014	The 30-day public comment period closed.
April 30, 2014	CMS convened a meeting of the Medicare Evidence Development & Coverage Advisory Committee concerning the use of LDCT screening for lung cancer.
November 10, 2014	CMS posted a proposed national coverage determination for screening for lung cancer with LDCT. A 30-day public comment period on the proposed decision began.
December 10, 2014	The 30-day public comment period on the proposed decision closed.
[posting date]	CMS posted the final national coverage determination.

V. Food and Drug Administration (FDA) Status

Currently, CT imaging systems and post-processing software go through the 510(k) process at the FDA to obtain clearance for commercial distribution. To obtain 510(k) clearance, the sponsor must demonstrate that the device is substantially equivalent to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (FDCA) that do not require approval of a premarket approval application (PMA).

CT devices were on the market prior to the passage of the Medical Device Amendments. They were originally indicated for general cross sectional imaging of the body. This includes the lungs and other specific organs. Subsequent modifications based on either additional built-in processing or on post-processing have expanded the breadth of CT images and with that, their use.

Counseling services are not generally under the purview of the FDA.

VI. General Methodological Principles

When making national coverage determinations concerning additional preventive services, CMS applies the statutory criteria in §1861(ddd) of the Social Security Act and regulations at 42 CFR 410.64, and evaluates relevant clinical evidence to determine whether or not the service is reasonable and necessary for the prevention or early detection of illness or disability, is recommended with a grade of A or B by the USPSTF, and is appropriate for individuals entitled to benefits under Part A or enrolled under Part B of the Medicare program.

CMS uses the initial public comments to inform its proposed national coverage determination. CMS responds in detail to the public comments on a proposed national coverage determination when issuing the final national coverage determination. Public comments sometimes cite published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. Public comments that contain personal health information will not be made available to the public.

VII. Evidence

A. Introduction

While a detailed discussion of screening is beyond the scope of this discussion, the basic parameters were established many years ago and are still well accepted to date. In 1968, Wilson and Jungner reported criteria to consider for screening:

- The condition being screened for should be an important health problem,
- The natural history of the condition should be well understood,
- There should be a detectable early stage,
- Treatment at an early stage should be of more benefit than at a later stage,
- A suitable test should be devised for the early stage,
- The test should be acceptable,
- Intervals for repeating the test should be determined,
- Adequate health service provision should be made for the extra clinical workload resulting from screening,
- The risks, both physical and psychological, should be less than the benefits,
- The costs should be balanced against the benefits.

(Wilson JMG, Jungner G. Principles and Practice of Screening for Disease. World Health Organization, 1968)

Health outcomes, benefits, and risks are important considerations. As Cochrane and Holland (1971) further noted, evidence on health outcomes, i.e., "evidence that screening can alter the natural history of disease in a significant proportion of those screened," is important in the consideration of screening tests since individuals are asymptomatic and "the practitioner initiates screening procedures."

The evaluation of screening tests has been largely standardized in the medical and scientific communities, and the "value of a screening test may be assessed according to the following criteria:

a. "*Simplicity*. In many screening programmes more than one test is used to detect one disease, and in a multiphasic programme the individual will be subjected to a number of tests within a short space of time. It is therefore essential that the tests used should be easy to administer and should be capable of use by para-medical and other personnel.
b. *Acceptability*. As screening is in most instances voluntary and a high rate of co-operation is necessary in an efficient screening programme, it is important that tests should be acceptable to the subjects.
c. *Accuracy*. The test should give a true measurement of the attribute under investigation.
d. *Cost*. The expense of screening should be considered in relation to the benefits resulting from the early detection of disease, i.e., the severity of the disease, the advantages of treatment at an early stage and the probability of cure.
e. *Precision* (sometimes called repeatability). The test should give consistent results in repeated trials.
f. *Sensitivity*. This may be defined as the ability of the test to give a positive finding when the individual screened has the disease or abnormality under investigation.
g. *Specificity*. This may be defined as the ability of the test to give a negative finding when the individual screened does not have the disease or abnormality under investigation".

(Cochrane A and Holland W. Validation of screening procedures. British Medical Bulletin 1971;27(1):3-8. PMID: 5100948).

B. United States Preventive Services Task Force (USPSTF)

The USPSTF recommendation for lung cancer screening with LDCT (December 2013) states:

- The USPSTF recommends annual screening for lung cancer with low-dose computed tomography in adults ages 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery. Grade: B recommendation.

The USPSTF assigns one of five letter grades to each of its recommendations (A, B, C, D, I). The following tables from the USPSTF website provide the current grade definitions and descriptions of levels of certainty. (http://www.uspreventiveservicestaskforce.org/uspstf/grades.htm)

Grade Definitions After July 2012

Grade	Definition	Suggestions for Practice
B		Offer or provide this service.

Grade	Definition	Suggestions for Practice
	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Level of Certainty	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	

Level of Certainty	Description
	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: The number, size, or quality of individual studies. Inconsistency of findings across individual studies. Limited generalizability of findings to routine primary care practice. Lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: The limited number or size of studies. Important flaws in study design or methods.

Level of Certainty	Description
	Inconsistency of findings across individual studies.
	Gaps in the chain of evidence.
	Findings not generalizable to routine primary care practice.
	Lack of information on important health outcomes.
	More information may allow estimation of effects on health outcomes.

* The USPSTF defines certainty as "likelihood that the USPSTF assessment of the net benefit of a preventive service is correct." The net benefit is defined as benefit minus harm of the preventive service as implemented in a general, primary care population. The USPSTF assigns a certainty level based on the nature of the overall evidence available to assess the net benefit of a preventive service.

C. Literature Search

CMS searched PubMed from May 2004 to August 2014. General keywords included screening low dose CT and lung cancer. Publications that presented original data on screening were considered. Abstracts, animal studies and non-English language publications were excluded.

D. Discussion of Evidence

Question 1: Is the evidence sufficient to determine that screening for lung cancer with low dose computed

tomography is recommended with a grade of A or B by the United States Preventive Services Task Force?

Question 2: Is the evidence sufficient to determine that screening for lung cancer with low dose computed tomography is reasonable and necessary for the prevention or early detection of illness or disability?

Question 3: Is the evidence sufficient to determine that screening for lung cancer with low dose computed tomography is appropriate for Medicare beneficiaries?

1. External technology assessments

Bach PB, Mirkin JN, Oliver TK, Azzoli CG, Berry DA, Brawley OW, Byers T, Colditz GA, Gould MK, Jett JR, Sabichi AL, Smith-Bindman R, Wood DE, Qaseem A, Detterbeck FC. Benefits and harms of CT screening for lung cancer: a systematic review. JAMA. 2012 Jun 13;307(22):2418-29. doi: 10.1001/jama.2012.5521. PMID: 22610500

Bach and colleagues reported the results of a systematic review of the evidence regarding the benefits and harms of lung cancer screening using LDCT. Studies were eligible "if they involved either an RCT using LDCT screening for lung cancer in one intervention group or a noncomparative cohort study of LDCT screening, provided they reported at least 1 of the following outcomes: lung cancer−specific or all-cause mortality, nodule detection rate, frequency of additional imaging, frequency of invasive diagnostic procedures (e.g., needle or bronchoscopic biopsy, surgical biopsy, surgical resection), complications from the evaluation of suspected lung cancer, or the rate of smoking cessation or reinitiation." Searching from 1996 to April 2012, eight randomized trials and 13 cohort studies met criteria. Three trials provided evidence on mortality. The NLST (NLST Team, 2012; n = 53,454) was a randomized trial that compared LDCT to chest radiography.

Table 4. Mortality Due to All Causes, Lung Cancer, and All Causes Other Than Lung Cancer in Randomized Trials: Rates and Relative Risk

Source	Events, No. (%)		Rate of Events per 100 000 Person-years		Relative Risk (95% CI)	Rate Ratio	Absolute Difference, %	No. Needed to Screen to Prevent 1 Event
	LDCT	Control	LDCT	Control				
All-Cause Mortality								
DANTE,[22] 2009	46 (3.6)	45 (3.8)	NR	NR	0.97 (0.80-1.20)[a,b]	NR	0.2	635
NLST,[23] 2011	1877 (7.0)	2000 (7.5)	1303[b]	1395[b]	0.93 (0.86-0.99)	0.93[b]	0.5	219
DLCST,[19] 2012	61 (3.0)	42 (2.0)	NR	NR	1.19 (1.01-1.40)	NR	–1.0	NR
Lung Cancer–Specific Mortality								
DANTE,[22] 2009	20 (1.6)	20 (1.7)	NR	NR	0.97 (0.71-1.32)[a,b]	NR	0.1	954
NLST,[23] 2011	356 (1.3)	443 (1.7)	247	309	0.80 (0.73-0.93)	0.80[b]	0.3	320
DLCST,[19] 2012	15 (0.7)	11 (0.5)	NR	NR	1.15 (0.83-1.61)	NR	–0.2	NR
Mortality Not Due to Lung Cancer								
DANTE,[22] 2009	26 (2.0)	25 (2.1)	NR	NR	0.99 (0.75-1.30)[b]	NR	0.1[b]	1898[b]
NLST,[23] 2011	1521 (5.7)	1557 (5.8)	1056[b]	1086[b]	0.99 (0.95-1.02)[b]	0.97[b]	0.1[b]	755[b]
DLCST,[19] 2012	46 (2.2)	31 (1.5)	NR	NR	1.20 (1.00-1.44)[b]	NR	–0.7[b]	NR

Abbreviations: DLCST, Danish Lung Cancer Screening Trial; NLST, National Lung Screening Trial; LDCT, low-dose computed tomography; NR, not reported.
[a] Based on count data.
[b] Calculated by authors.

Table 4. Page 2422. JAMA. 2012 Jun 13;307(22):2418-29.

The authors concluded: "Screening a population of individuals at a substantially elevated risk of lung cancer most likely could be performed in a manner such that the benefits that accrue to a few individuals outweigh the harms that many will experience. However, there are substantial uncertainties regarding how to translate that conclusion into clinical practice."

Humphrey LL, Teutsch S, Johnson M; U.S. Preventive Services Task Force. Lung cancer screening with sputum cytologic examination, chest radiography, and computed tomography: an update for the U.S. Preventive Services Task Force. Ann Intern Med. 2004 May 4;140(9):740-53. PMID: 15126259

Humphrey and colleagues reported the results of a systematic evidence review on lung cancer screening that provided the evidence base for the 2004 USPSTF recommendation. Studies on lung cancer screening using sputum cytology, chest radiology and computed tomography were reviewed. For LDCT, several observational studies were reviewed (presented in Table 4). There were no randomized controlled trials.

Table 4. **Outcomes of Lung Cancer Screening with Low-Dose Computed Tomography***

Study, Year (Reference)	Screening Interval	Screening Type	Screening Tests Performed	Positive Test Results	Recommendation for Follow-up Based on LDCT			Surgery for Diagnosis (Benign Nodules)	Lung Cancer†	Stage 1 Disease
					HRCT	Referral	Biopsy			
	mo		*n*	*n (%)*	← *n* →			*n (n)*	*n (%)*	*%*
Diederich et al., 2002 (53)		Baseline	817	350 (43)	269	29	13	1 (1)	11 (1.3) (1 interval)	58
Henschke et al., 1999, 2001 (54, 55)	6–18	Baseline LDCT	1000	237 (24)	233	104	27	0	31 (3.1)	85
		Incidence LDCT	1184	40	40	NR	9	NR	9 (0.9)	67
		Baseline CXR	1000	68 (6.8)	33	NR	NR	0	7 (0.7)	
		CXR after LDCT		33 (3.3)						
Nawa et al., 2002 (56)	12	Baseline LDCT	7956	2099 (26.4)	541	64	NR	NR	36 (0.5)	86
		Incidence LDCT	5568	NR	148	7	NR	NR	4 (0.1)	100
Sone et al., 2001 (58)	12	Baseline LDCT	5483	279 (5.1)	266	NR	NR	NR (7)	22 (0.4)	100
		Incidence LDCT	8303†	309	297	NR	NR	NR (9)	37 (0.6)	86
Sobue et al., 2002 (59)	6	Baseline LDCT	1611	186 (11.5)	186	25	21	0	13 (0.8)	77
		Incidence LDCT	7891	721	721	57	35	1 (0)	19 (0.2)	79
		Baseline CXR	1611	55 (3.4)	22	9	8	0	5 (0.3)	60
		Incidence CXR	7891	202	89	7	4	0	3 (0.2)	0
Swensen et al., 2002, 2003 (61, 62)	12	Baseline LDCT	1520	782 (51.4)	NR	NR	NR		27 (1.8)‡	
		Combined data						NR (8)		66
		Incidence LDCT	2916	336	NR	NR	NR		11 (0.7) (+2 interval)‡	

* All data are presented by individual except incidence, which refers to screening tests performed. CXR = chest radiography; HRCT = high-resolution computed tomography; LDCT = low-dose computed tomography; NR = not reported.
† Percentage of lung cancer for incidence = cases of lung cancer identified with incidence screening/cases of lung cancer in cohort minus cases of prevalence cancer.
‡ 1 case of malignant disease diagnosed with sputum cytologic examination only.

Table 4. Humphrey et al. Ann Intern Med. 2004 May 4;140(9):747. www.annals.org

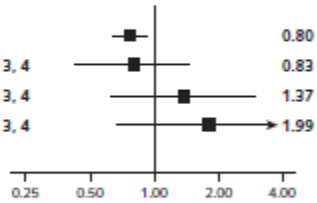
Humphrey and colleagues concluded: "Current data do not support screening for lung cancer with any method. These data, however, are also insufficient to conclude that screening does not work, particularly in women. Two randomized trials of screening with chest radiography or low-dose CT are currently under way and will better inform lung cancer screening decisions."

Humphrey LL, Deffebach M, Pappas M, Baumann C, Artis K, Mitchell JP, Zakher B, Fu R, Slatore CG. Screening for lung cancer with low-dose computed tomography: a systematic review to update the US Preventive Services Task Force recommendation. Ann Intern Med. 2013 Sep 17;159(6):411-20. doi: 10.7326/0003-4819-159-6-201309170-00690. PMID: 23897166

Humphrey and colleagues reported the results of a systematic review to re-evaluate the effectiveness of LDCT screening for lung cancer for the USPSTF. Trials and cohort studies that evaluated screening or treatment interventions for lung cancer that reported health outcomes were eligible. Searching from 2000 to May 2013, seven trials met criteria, with four trials that were included in the review because they reported results for both intervention and control groups. The NLST (NLST team, 2012; n = 53,454) compared LDCT to chest radiography. The authors stated: "One large good-quality trial reported that screening was associated with significant reductions in lung cancer (20 %) and all-cause (6.7 %) mortality. Three small European trials showed no benefit of screening. Harms included radiation exposure, overdiagnosis, and a high rate of false positive findings that typically were resolved with further imaging. Smoking cessation was not affected. Incidental findings were common."

Figure 1. Trial results for lung cancer mortality.

Study, Year (Reference)	Male, %	Follow-up, *y*	Deaths per 100 000 Person-Years, *n*		Mean Age, *y*	Pack-Years, *n*	Screening Intervals, *y*	Relative Risk (95% CI)
			Intervention	Control				
NLST, 2011 (53)	59	6.5	247	309	61	56	0, 1, 2	0.80 (0.73–0.93)
DANTE, 2009, 2008 (39, 40)	100	2.8	527	637	65	47	0, 1, 2, 3, 4	0.83 (0.45–1.54)
DLCST, 2012 (60)	56	4.8	154	112	58	36	0, 1, 2, 3, 4	1.37 (0.63–2.97)
MILD, 2012 (57)*	66	4.4	216	109	57†	39†	0, 1, 2, 3, 4	1.99 (0.80–4.96)



DANTE = Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays; DLCST = Danish Lung Cancer Screening Trial; MILD = Multicentric Italian Lung Detection; NLST = National Lung Screening Trial.
* Annual screening group compared only with control group; biennial screening group not shown.
† Median.

Figure 1. Page 414. Ann Intern Med. 2013 Sep 17;159(6):411-20.

The authors concluded: "Strong evidence shows that LDCT screening can reduce lung cancer and all-cause mortality. The harms associated with screening must be balanced with the benefits."

Manser R, Lethaby A, Irving LB, Stone C, Byrnes G, Abramson MJ, Campbell D. Screening for lung cancer. Cochrane Database Syst Rev. 2013 Jun 21;6:CD001991. doi: 10.1002/14651858.CD001991.pub3. PMID: 23794187

Manser and colleagues reported the results of a Cochrane systematic review "to determine whether screening for lung cancer, using regular sputum examinations, chest radiography or CT scanning of the chest, reduces lung cancer mortality." Controlled trials were included. This report updated the original review performed in 1999.

The authors reported: "We included nine trials in the review (eight randomised controlled studies and one controlled trial) with a total of 453,965 subjects. In one large study that included both smokers and non-smokers comparing annual chest x-ray screening with usual care there was no reduction in lung cancer mortality (RR 0.99, 95 % CI 0.91 to 1.07). In a meta-analysis of studies comparing different frequencies of chest x-ray screening, frequent screening with chest x-rays was associated with an 11 % relative increase in mortality from lung cancer compared with less frequent screening (RR 1.11, 95 % CI 1.00 to 1.23); however several of the trials included in this meta-analysis had potential methodological weaknesses. We observed a non-statistically significant trend to reduced mortality from lung cancer when screening with chest x-ray and sputum cytology was compared with chest x-ray alone (RR 0.88, 95% CI 0.74 to 1.03). There was one large methodologically rigorous trial in high-risk smokers and ex-smokers (those aged 55 to 74 years with ≥ 30 pack-years of smoking and who quit ≤ 15

years prior to entry if ex-smokers) comparing annual low-dose CT screening with annual chest x-ray screening; in this study the relative risk of death from lung cancer was significantly reduced in the low-dose CT group (RR 0.80, 95% CI 0.70 to 0.92)."

Screening for lung cancer (Review)
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Annual low dose CT screening versus annual chest x-ray for lung cancer

Patient or population: Patients with lung cancer
Settings:
Intervention: Annual low-dose CT screening versus annual chest x-ray

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Annual low-dose CT screening versus annual chest x-ray				
Lung cancer mortality	17 per 1000	13 per 1000 (12 to 15)	RR 0.8 (0.7 to 0.92)	53454 (1 study)	⊕⊕⊕⊕ high	
All-cause mortality	75 per 1000	70 per 1000 (66 to 75)	RR 0.94 (0.88 to 1)	53454 (1 study)	⊕⊕⊕⊕ high	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Page 19. Cochrane Database Syst Rev. 2013 Jun 21;6:CD001991.

The authors concluded: "The current evidence does not support screening for lung cancer with chest radiography or sputum cytology. Annual low-dose CT screening is associated with a reduction in lung cancer mortality in high -risk smokers but further data are required on the cost effectiveness of screening and the relative harms and benefits of screening across a range of different risk groups and settings."

Prosch H, Schaefer-Prokop C. Screening for lung cancer. Curr Opin Oncol. 2014 Mar;26(2):131-7. doi: 10.1097/CCO.0000000000000055. PMID: 24441507

Prosch and Schaefer-Prokop performed a systematic review of recent randomized controlled trials of lung cancer screening using LDCT. Included trials were the NLST, the Detection And screening of early lung cancer by Novel imaging TEchnology and molecular assays (DANTE) trial, the Multicentric Italian Lung Detection (MILD) trial, and the Danish Lung Cancer Screening Trial (DLCST). They reported: "The National Lung Screening Trial (NLST) was the first study that provided statistical evidence that LD-CT screening for lung cancer significantly reduces lung

cancer mortality by 20 %. Three statistically underpowered European trials could not confirm the positive effect of LD-CT screening on lung cancer mortality. Major obstacles in lung cancer screening are overdiagnosis and the large number of false positive results. In the NLST, more than 24 % of the screens were positive, most of which (96.4 %) proved to be benign in nature. Optimized protocols for the workup of detected nodules may help to reduce the number of false-positive screens." They further noted: "Long-term follow-up data are still anticipated on the European screening trials. Furthermore, data on the extent of the potential dangers of LD-CT screening, such as overdiagnosis, false-positive results, and the effect of cumulative radiation dose, have yet to be investigated thoroughly."

Table 1. Ongoing European randomized controlled low-dose computed tomography screening trials

Trial	DANTE [9]	NELSON [10]	ITALUNG [11]	DLCST [12]	MILD [13]	LUSI [14]	UKLS [15]
Country	Italy	The Netherlands, Belgium	Italy	Denmark	Italy	Germany	Great Britain
Start of trial	2001	2003	2004	2004	2005	2007	2012
Included persons	2811	15822	3206	4104	4099	4052	32000 planned
Screening rounds	5	4	5	5	10	5	1
Screening intervals	1 year	1, 3, and 5 years	1 year	1 year	1 or 2 years (randomized)	1 year	–
Age range (years)	60–75	50–75	55–70	50–70	>49	50–69	50–75
Pack-years	≥20	>15	≥20	≥20	≥20	>15	
Years since quitting	<10	≤10	<10	<10	<10	<10	
Recruitment completed	Yes	Yes	Yes	Yes	No	Yes	No
Screening completed	Yes	No	Yes	Yes	Yes	No	No

DANTE, Detection And screening of early lung cancer by Novel imaging TEchnology and molecular assays; DLCST, Danish Lung Cancer Screening Trial; ITALUNG, Italian Lung Cancer Computed Tomography Screening Trial; LUSI, Lung Screening Intervention; MILD, Multicentric Italian Lung Detection; NELSON, Nederlands-Leuvens Longkanker Screenings Onderzoek; UKLS, United Kingdom Lung Screen.

Table 1. Page 133. Curr Opin Oncol. 2014 Mar;26(2):131-7.

2. Internal technology assessment

Infante M, Cavuto S, Lutman FR, Brambilla G, Chiesa G, Ceresoli G, Passera E, Angeli E, Chiarenza M, Aranzulla G, Cariboni U, Errico V, Inzirillo F, Bottoni E, Voulaz E, Alloisio M, Destro A, Roncalli M, Santoro A, Ravasi G; DANTE Study Group. A randomized study of lung cancer screening with spiral computed tomography: three-year results from the DANTE trial. Am J Respir Crit Care Med. 2009 Sep 1;180(5):445-53. doi: 10.1164/rccm.200901-0076OC. Epub 2009 Jun 11. PMID: 19520905

Infante and colleagues reported results of the DANTE randomized trial designed "to explore the effect of screening with low-dose spiral computed tomography (LDCT) on lung cancer mortality." Men aged 60 to 74 years with ≥ 20 pack-years smoking history were eligible. Patients with comorbidities that limited life expectancy to < 5 years, had a previous history of malignancy, or who were unable to comply with study protocols were excluded. Primary outcome was lung cancer mortality. Secondary outcomes included all-cause mortality, lung cancer incidence, stage and resectability. Between March 2001 and February 2006, 2811 participants were randomly assigned and 2472 were enrolled to yearly LDCT screening for four years (n = 1276) or yearly medical care control (n = 1196) at three sites in Italy. Mean age was 64 years. About 56 % were active smokers at baseline. Median follow-up was 33.7 months. Mean pack-years smoking was 47.

The authors reported 20 (1.6 %) lung cancer deaths in the LDCT group and 20 (1.7 %) in the control group (p = 0.84) and 46 (3.6 %) total deaths in the LDCT group and 45 (3.8 %) in the control group (p = 0.83). They concluded: "possible overdiagnosis, false positives, hazards of downstream investigation procedures, and cost issues make the results of randomized studies critically important in establishing a proper public health policy, and the final results from all ongoing randomized trials are awaited. In the meantime, continued application of current policies is supported by our data, and screening for LC with LDCT should not be advertised or proposed to high-risk subjects outside research programs."

National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, Gareen IF, Gatsonis C, Marcus PM, Sicks JD. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011 Aug 4;365(5):395-409. doi: 10.1056/NEJMoa1102873. Epub 2011 Jun 29. PMID: 21714641

The NCI-sponsored NLST was a randomized trial "to determine whether screening with low-dose CT, as compared with chest radiography, would reduce mortality from lung cancer among high-risk persons." From August 2002 to April 2004, 53,454 individuals who were "between 55 and 74 years of age at the time of randomization, had a history of cigarette smoking of at least 30 pack-years, and, if former smokers, had quit within the previous 15 years" were enrolled at 33 U.S. centers and randomized to screening with 3 annual LDCT (n = 26,722) or three annual chest radiography (n = 26,732). Individuals who "had previously received a diagnosis of lung cancer, had undergone chest CT within 18 months before enrollment, had hemoptysis, or had an unexplained weight loss of more than 6.8 kg (15 lb) in the preceding year were excluded." All screening tests were performed and interpreted according to protocol (NLST study design, 2011). It was "estimated that each NLST low-dose CT resulted in an average effective dose of 1.5 mSv, whereas the effective dose from conventional chest CT varies considerably in clinical practice but is on the order of 8 mSv" (NLST study design, 2011). The primary outcome was lung cancer mortality. Secondary outcomes included all-cause mortality and lung cancer incidence. Median age was approximately 61 years with 26.6 % of participants being 65 years and older. Men comprised 59 % of the study. Ninety one percent were white. Forty eight percent were current smokers. Median follow-up was 6.5 years. Adherence to all three screenings was 95 % in the LDCT group and 93 % in the radiography group.

The authors reported "[t]here were 247 deaths from lung cancer per 100,000 person-years in the low-dose CT group and 309 deaths per 100,000 person-years in the radiography group, representing a relative reduction in mortality from lung cancer with low-dose CT screening of 20.0 % (95 % CI, 6.8 to 26.7; P = 0.004). The rate of death from any cause was reduced in the low-dose CT group, as compared with the radiography group, by 6.7 % (95 % CI, 1.2 to 13.6; P = 0.02)."

Table 7. Cause of Death on the Death Certificate, According to Screening Group.*

Cause of Death	Low-Dose CT Group	Radiography Group	Total
		number/total number (percent)	
Neoplasm of bronchus and lung†	427/1865 (22.9)	503/1991 (25.3)	930/3856 (24.1)
Other neoplasm	416/1865 (22.3)	442/1991 (22.2)	858/3856 (22.3)
Cardiovascular illness	486/1865 (26.1)	470/1991 (23.6)	956/3856 (24.8)
Respiratory illness	175/1865 (9.4)	226/1991 (11.4)	401/3856 (10.4)
Complications of medical or surgical care	12/1865 (0.6)	7/1991 (0.4)	19/3856 (0.5)
Other	349/1865 (18.7)	343/1991 (17.2)	692/3856 (17.9)

* A total of 3875 death certificates were received (1877 for participants in the low-dose CT group and 1998 for those in the radiography group), but the cause of death was unknown for 12 participants in the low-dose CT group and 7 in the radiography group. The denominators represent only the deaths for which the cause was known. Causes of death were categorized according to the following codes in the *International Classification of Diseases, 10th Revision* (ICD-10): neoplasms of bronchus and lung, C33-C34; neoplasms other than bronchus and lung, C00-D48 (excluding C33 and C34); cardiovascular illness, I00-I99; respiratory illness, J00-J99; complications of medical or surgical care, S00-T17.8, T18-T99, and Y40-Y84; unknown, R96-R99 and death certificates without a coded cause of death; and other, all remaining codes.

† The number of deaths from neoplasm of the bronchus and lung in this table is not equal to the number of lung-cancer deaths in the lung-cancer mortality analysis. The lung-cancer deaths included here are those that were determined from information on the death certificate only (without review by the end-point verification team) and include deaths that occurred through December 31, 2009.

Table 7. page 407. N Engl J Med. 2011 Aug 4;365(5):395-409.

The authors concluded "[s]creening with the use of low-dose CT reduces mortality from lung cancer."

Pastorino U, Rossi M, Rosato V, Marchianò A, Sverzellati N, Morosi C, Fabbri A, Galeone C, Negri E, Sozzi G, Pelosi G, La Vecchia C. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. Eur J Cancer Prev. 2012 May;21(3):308-15. doi: 10.1097/CEJ.0b013e328351e1b6. PMID: 22465911

Pastorino and colleagues reported the results of the MILD randomized trial "to evaluate the impact on mortality of early lung cancer detection through LDCT at annual or biennial intervals versus no screening." Individuals who were ≥ 49 years of age with ≥ 20 pack-year smoking history and no history of cancer within the past five years were included. No other exclusion criteria were reported. From September 2005 to January 2011, 4099 participants were enrolled and randomly assigned to annual LDCT screening (n = 1190), biennial LDCT screening (n = 1186) and no screening control group with smoking cessation interventions and pulmonary function tests (n = 1723) at one site in Italy (trial was initially designed to be conducted at multiple centers but limited to one site due to funding). Primary outcome was lung cancer mortality. Secondary outcomes included all-cause mortality and lung cancer incidence. Median age was 57 years. Men comprised 67 % of the study population. At baseline, there were more current smokers in the control group (89.7 %) compared to the LDCT screening groups (68.3 % annual and 68.9 % biennial). Median pack-years smoking was 39.

The authors reported: "The cumulative 5-year lung cancer incidence rate was 311/100 000 in the control group, 457 in the biennial, and 620 in the annual LDCT group (P = 0.036); lung cancer mortality rates were 109, 109, and 216/100 000 (P = 0.21), and total mortality rates were 310, 363, and 558/100 000, respectively (P = 0.13)." They concluded: "There was no evidence of a protective effect of annual or biennial LDCT screening. Furthermore, a meta-analysis of the four published randomized trials [DANTE (Infante), DLCST (Saghir), MILD, NLST] showed similar overall mortality in the LDCT arms compared with the control arm." "The effect on lung cancer mortality remains significant (relative risk 0.82, 95 % CI 0.73 – 0.93) but the value of disease-specific mortality as the only endpoint appears questionable for two reasons: the assessment of the real cause of death can be very difficult in heavy smokers because of complex comorbidity; a shift in the cause of death from one disease to another is frequent in screened populations and hence potentially misleading."

Saghir Z1, Dirksen A, Ashraf H, Bach KS, Brodersen J, Clementsen PF, Døssing M, Hansen H, Kofoed KF, Larsen KR, Mortensen J, Rasmussen JF, Seersholm N, Skov BG, Thorsen H, Tønnesen P, Pedersen JH. CT screening for lung cancer brings forward early disease. The randomised Danish Lung Cancer Screening Trial: status after five annual screening rounds with low-dose CT. Thorax. 2012 Apr;67(4):296-301. doi: 10.1136/thoraxjnl-2011-200736. Epub 2012 Jan 27.PMID: 22286927.

Saghir and colleagues reported the results of a randomized controlled trial "to evaluate if annual low dose CT screening [for 5 annual screenings] can reduce lung cancer mortality by more than 25 %" (Pederson, 2009). Inclusion criteria were age 50-70 years, current or former smokers with at least 20 pack-years of smoking history, ability to climb two flights of stairs (36 steps) without pausing. Exclusion criteria were "weight over 130 kg, history of cancer diagnosis and treatment, lung tuberculosis, illness that would shorten life expectancy to < 10 years and chest CT received during the last year for any reason." Primary outcome was lung cancer mortality. Secondary outcomes included overall mortality, number of lung cancers, stage and health economic evaluations. From October 2004 to March 2006, 4104 participants were enrolled and randomly assigned to CT screening group (five annual LDCT; n = 2052) or control group (no screening) (n = 2052) at one site in Denmark. "All participants had an annual visit at the screening clinic, where lung function tests were performed, and questionnaires concerning health, lifestyle, smoking habits and psychosocial consequences of screening were completed." Median age was not reported (peak number of patients were between 55-59 years). Men comprised 55 % of the study population. Median follow-up was 4.81 years.

The authors reported: "At the end of screening, 61 patients died in the screening group and 42 in the control group (p = 0.059). 15 and 11 died of lung cancer, respectively (p = 0.428)." They concluded: "CT screening for lung cancer brings forward early disease, and at this point no stage shift or reduction in mortality was observed. More lung cancers were diagnosed in the screening group, indicating some degree of over diagnosis and need for longer follow-up."

3. Medicare Evidence Development & Coverage Advisory Committee (MEDCAC)

On April 30, 2014, a Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) meeting was convened to discuss the body of evidence, hear presentations, consider public comments, and make recommendations to CMS regarding the currently available evidence related to early detection (screening) of lung cancer with LDCT in asymptomatic adults with histories of significant smoking. A CMS representative presented a basic background of lung cancer screening; how Medicare's consideration of preventive services is statutorily

different than CMS' consideration of evaluation and management services; and read the voting and discussion questions that would be considered by the panel. The panel heard presentations from four invited guest speakers, 16 scheduled speakers, and four members of the public.

The eight voting members on the panel voted on three questions (listed below) using a scale of one to five, with one representing a low confidence vote and five representing a high confidence vote. An average voting score of 2.5 represented intermediate confidence. The scores of the voting panel members were recorded and the average was calculated.

1. How confident are you that there is adequate evidence to determine if the benefits outweigh the harms of lung cancer screening with LDCT [CT acquisition variables set to reduce exposure to an average effective dose of 1.5 mSv…] in the Medicare population?
    - Average score: **2.22**

2. How confident are you that the harms of lung cancer screening with LDCT (average effective dose of 1.5 mSv) if implemented in the Medicare population will be minimized?
    - Average score: **2.33**

3. How confident are you that clinically significant evidence gaps remain regarding the use of LDCT (average effective dose of 1.5 mSv) for lung cancer screening in the Medicare population outside a clinical trial?
    - Average score: **4.67**. Since the resulting average voting score on this question showed at least intermediate confidence (score ≥ 2.5), the panel was asked to discuss any significant gaps identified and how CMS might support their closure.

Information about the meeting, including the agenda, presentations from speakers, transcripts, and results of the voting questions are available on the CMS Website at: http://www.cms.gov/medicare-coverage-database/details/medcac-meeting-details.aspx?MEDCACId=68.

4. Evidence-based guidelines

Detterbeck FC, Mazzone PJ, Naidich DP, Bach PB. Screening for lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013 May;143(5 Suppl):e78S-92S. doi: 10.1378/chest.12-2350. PMID: 23649455

Detterbeck and colleagues reported the American College of Chest Physicians guidelines based in part on the systematic review by Bach (2012). Specifically for lung cancer screening with LDCT:

"3.4.1. For smokers and former smokers who are age 55 to 74 and who have smoked for 30 pack-years or more and either continue to smoke or have quit within the past 15 years, we suggest that annual screening with LDCT should be offered over both annual screening with CXR or no screening, but only in settings that can deliver the comprehensive care provided to NLST participants (Grade 2B)." The guidelines also included the following remarks.

- "Counseling should include a complete description of potential benefits and harms, so the individual can decide whether to undergo LDCT screening."
- "Screening should be conducted in a center similar to those where the NLST was conducted, with multidisciplinary coordinated care and a comprehensive process for screening, image interpretation, management of findings, and evaluation and treatment of potential cancers."
- "A number of important questions about screening could be addressed if individuals who are screened for lung cancer are entered into a registry that captures data on follow-up testing, radiation exposure, patient experience, and smoking behavior."
- "Quality metrics should be developed such as those in use for mammography screening, which could help enhance the benefits and minimize the harm for individuals who undergo screening."
- "Screening for lung cancer is not a substitute for stopping smoking. The most important thing patients can do to prevent lung cancer is not smoke."
- "The most effective duration or frequency of screening is not known."

U.S. Preventive Services Task Force. Lung cancer screening: recommendation statement. Ann Intern Med. 2004 May 4;140(9):738-9. PMID: 15126258

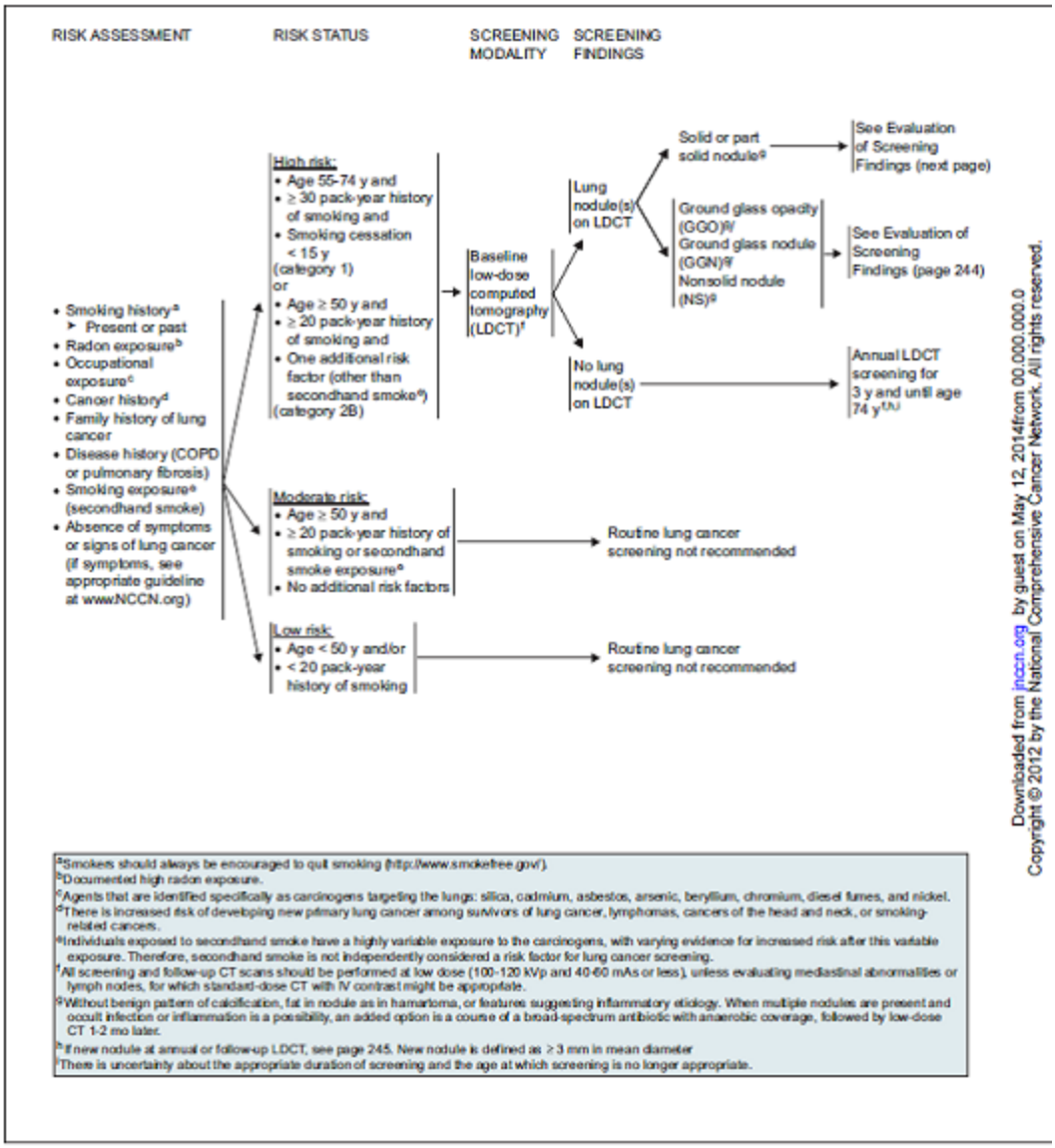
In 2004, the USPSTF concluded that "the evidence is insufficient to recommend for or against screening asymptomatic persons for lung cancer with either low-dose computerized tomography (LDCT), chest x-ray (CXR), sputum cytology, or a combination of these tests. This is a grade I recommendation." As reported in the analysis, "The USPSTF found fair evidence that screening with LDCT, CXR or sputum cytology can detect lung cancer at an earlier stage than lung cancer would be detected in an unscreened population; however, the USPSTF found poor evidence that any screening strategy for lung cancer decreases mortality. Because of the invasive nature of diagnostic testing and the possibility of a high number of false-positive tests in certain populations, there is potential for significant harms from screening. Therefore, the USPSTF could not determine the balance between the benefits and harms of screening for lung cancer."

Moyer VA; U.S. Preventive Services Task Force. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014 Mar 4;160(5):330-8. doi: 10.7326/M13-2771. PMID: 24378917

Moyer, on behalf of the USPSTF, reported a revised recommendation on lung cancer screening based on the review by Humphrey, et al. (2013) (see external technology assessments section above), concluding that "[t]he USPSTF recommends annual screening for lung cancer with low-dose computed tomography (LDCT) in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery. (B recommendation)"

Wood DE, Eapen GA, Ettinger DS, Hou L, Jackman D, Kazerooni E, Klippenstein D, Lackner RP, Leard L, Leung AN, Massion PP, Meyers BF, Munden RF, Otterson GA, Peairs K, Pipavath S, Pratt-Pozo C, Reddy C, Reid ME, Rotter AJ, Schabath MB, Sequist LV, Tong BC, Travis WD, Unger M, Yang SC. Lung cancer screening. J Natl Compr Canc Netw. 2012 Feb;10(2):240-65. PMID: 22308518

Wood and colleagues reported the National Comprehensive Cancer Network® (NCCN®) guideline and consensus statement. The lung cancer panel recommended "helical LDCT screening for select patients at high risk for lung cancer based on the NLST results, nonrandomized studies, and observational data." (2012)



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Page 242. © JNCCN–Journal of the National Comprehensive Cancer Network | Volume 10 Number 2 | February 2012.

5. Professional Society Recommendations

American Academy of Family Physicians. Lung cancer clinical recommendations. Accessed May 12, 2014. Available at: http://www.aafp.org/patient-care/clinical-recommendations/all/lung-cancer.html.

The AAFP concluded that "the evidence is insufficient to recommend for or against screening for lung cancer with low-dose computed tomography (LDCT) in persons at high risk for lung cancer based on age and smoking history. (2013) (Grade: I recommendation)"

American Lung Association. Providing guidance on lung cancer screening to patients and physicians. April 23, 2012. Accessed May 12, 2014. Available at: http://www.lung.org/lung-disease/lung-cancer/lung-cancer-screening-guidelines/lung-cancer-screening.pdf

The American Lung Association "convened a Lung Cancer Screening Committee, chaired by Jonathan Samet, MD, MS, to review the current scientific evidence on cancer screening in order to assist the ALA in offering the best possible guidance to the public and those suffering from lung disease." "The Committee acknowledges that cancer screening is associated with both benefits and risks and unfortunately, the NLST could not answer a number of questions on the advantages and safety of screening in the general population. In spite of this, the Committee provides the following interim recommendations:

- The best way to prevent lung cancer caused by tobacco use is to never start or quit smoking.
- Low-dose CT screening should be recommended for those people who meet NLST criteria:
    - current or former smokers, aged 55 to 74 years
    - a smoking history of at least 30 pack-years
    - no history of lung cancer
- Individuals should not receive a chest X-ray for lung cancer screening
- Low-dose CT screening should NOT be recommended for everyone
- ALA should develop public health materials describing the lung cancer screening process in order to assist patients in talking with their doctors. This educational portfolio should include information that explains and clarifies for the public:
    - the difference between a screening process and a diagnostic test
    - the benefits, risks and costs (emotional, physical and economic)
    - that not all lung cancers will be detected through use of low dose CT scanning
- A call to action should be issued to hospitals and screening centers to:
    - establish ethical policies for advertising and promoting lung cancer CT screening services
    - develop educational materials to assist patients in having careful and thoughtful discussions between patients and their physicians regarding lung cancer screening
    - provide lung cancer screening services with access to multidisciplinary that can deliver the needed follow-up for evaluation of nodules."

Jaklitsch MT, Jacobson FL, Austin JH, Field JK, Jett JR, Keshavjee S, MacMahon H, Mulshine JL, Munden RF, Salgia R, Strauss GM, Swanson SJ, Travis WD, Sugarbaker DJ. The American Association for Thoracic Surgery guidelines for lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups. J Thorac Cardiovasc Surg. 2012 Jul;144(1):33-8. doi: 10.1016/j.jtcvs.2012.05.060. PMID: 22710039

Jaklitsch and colleagues reported American Association for Thoracic Surgery guidelines for lung cancer screening using LDCT. "The American Association for Thoracic Surgery guidelines call for annual lung cancer screening with low-dose computed tomography screening for North Americans from age 55 to 79 years with a 30 pack-year

history of smoking. Long-term lung cancer survivors should have annual low-dose computed tomography to detect second primary lung cancer until the age of 79 years. Annual low-dose computed tomography lung cancer screening should be offered starting at age 50 years with a 20 pack-year history if there is an additional cumulative risk of developing lung cancer of 5 % or greater over the following 5 years. Lung cancer screening requires participation by a subspecialty-qualified team. The American Association for Thoracic Surgery will continue engagement with other specialty societies to refine future screening guidelines."

Kazerooni EA, Armstrong MR, Amorosa JK, Hernandez D, Liebscher LA, Nath H, McNitt-Gray MF, Stern EJ, Wilcox PA. ACR CT Accreditation Program and the Lung Cancer Screening Program Designation. J Am Coll Radiol. 2014 Nov 20. pii: S1546-1440(14)00633-4. doi: 10.1016/j.jacr.2014.10.002. [Epub ahead of print] PMID: 25455196

The authors reported the current position statement of the American College of Radiology: "The ACR strongly supports the use of LDCT for lung cancer screening and believes that the ability of this technique to reduce mortality depends on appropriate patient selection, the performance of high-quality, low–radiation exposure LDCT examinations interpreted by qualified physicians, and a structured reporting and management system as the foundation for quality reporting and outcomes monitoring. Building on extensive ACR experience with breast cancer screening, including the comprehensive widespread use of BI-RADS®, imaging accreditation, quality metrics, and both clinical and research registries, the ACR has focused on expeditiously bringing tools to practicing radiologists to promote the dissemination of high-quality lung cancer screening.

The ACR-Society of Thoracic Radiology (STR) Practice Parameter for the Performance and Reporting of Lung Cancer Screening Thoracic CT 2014 (Resolution 4) provides guidance on indications and contraindications, specifications of the examination, interpretation and reporting, documentation and communication, and equipment specifications. The first edition of the ACR's Lung-RADS presents a structured management, reporting, and audit schema for lung cancer screening practice and quality assurance (QA). In addition, the ACR has collected lung cancer screening resources on a single web page for individuals, practices, and institutions. Provided links include the 2014 CT protocols from The American Association of Physicists in Medicine, and smoking cessation resources, an important component of any lung cancer screening program. Lastly, as part of the ACR suite of registries under the National Radiology Data Registry, the ACR will launch the Lung Cancer Screening Practice Registry in early 2015. Use of the registry will enable providers to perform clinical practice audits and compare their cancer detection rates, false positives, and positive predictive value rates against benchmarks similar to the standards used in mammography. Participation will be very useful for assuring quality in individual radiology practices."

Table 5. ACR Lung Cancer Screening Center designation: additional requirements for the ACR CT Accreditation with chest module

- Definition of eligible and appropriate screening population
- Incorporation of smoking cessation
- Physician qualification of at least 200 chest CT exams in the prior 36 months
- Structured reporting and management tool, such as Lung-RADS
- Multidetector, helical (spiral) scanner; low-dose CT protocol must have a $CTDI_{vol}$ of $\leq$3 mGy for a standard-size patient (5'7"; 154 lb)
- Exposure techniques must be adjusted for patient size
- Participation in the ACR Dose Index Registry is recommended
- Use and submit a low-dose CT protocol that meets the criteria outlined in the ACR- Society of Thoracic Radiology Practice Parameter for the Performance and Reporting of Lung Cancer Screening Thoracic CT

Note: $CTDI_{vol}$ = CT dose index volume.

Table 5. Kazerooni et al. J Am Coll Radiol. 2014 Nov 20. pii: S1546-1440(14)00633-4. doi: 10.1016/j.jacr.2014.10.002. [Epub ahead of print] PMID: 25455196

Mazzone P, Powell CA, Arenberg D, Bach P, Detterbeck F, Gould M, Jaklitsch MT, Jett J, Naidich D, Vachani A, Wiener RS, Silvestri G. Components Necessary for High Quality Lung Cancer Screening: American College of Chest Physicians and American Thoracic Society Policy Statement. Chest. 2014 Oct 30. doi: 10.1378/chest.14-2500. [Epub ahead of print] PMID: 25356819

The authors presented a joint position statement endorsed by the American College of Chest Physicians, American Thoracic Society, American Association of Thoracic Surgery, American Cancer Society, and American Society of Preventive Oncology: "Lung cancer screening with a low dose chest CT scan can result in more benefit than harm when performed in settings committed to developing and maintaining high quality programs. This project aimed to identify the components of screening that should be a part of all lung cancer screening programs. To do so, committees with expertise in lung cancer screening were assembled by the Thoracic Oncology Network of the ACCP and the Thoracic Oncology Assembly of the ATS. Lung cancer program components were derived from evidence-based reviews of lung cancer screening, and supplemented by expert opinion. This statement was developed and modified based on iterative feedback of the committees. Nine essential components of a lung cancer screening program were identified. Within these components twenty one Policy Statements were developed and translated into criteria that could be used to assess the qualification of a program as a screening facility. Two additional Policy Statements related to the need for multi-society governance of lung cancer screening were developed. High quality lung cancer screening programs can be developed within the presented framework of nine essential program components outlined by our committees." The components are:

Component 1: Who is offered lung cancer screening;
Component 2: How often, and for how long, to screen;
Component 3: How the CT is performed;
Component 4: Lung nodule identification;
Component 5: Structured reporting;
Component 6: Lung nodule management algorithms;
Component 7: Smoking cessation;
Component 8: Patient and provider education;
Component 9: Data collection;

Wender R, Fontham ET, Barrera E Jr, Colditz GA, Church TR, Ettinger DS, Etzioni R, Flowers CR, Gazelle GS, Kelsey DK, LaMonte SJ, Michaelson JS, Oeffinger KC, Shih YC, Sullivan DC, Travis W, Walter L, Wolf AM, Brawley OW, Smith RA. American Cancer Society lung cancer screening guidelines. CA Cancer J Clin. 2013 Mar-Apr;63(2):107-17. doi: 10.3322/caac.21172. Epub 2013 Jan 11. PMID: 23315954

In 2013, Wender and colleagues, on behalf of the American Cancer Society, released lung cancer screening guidelines: "Findings from the National Cancer Institute's National Lung Screening Trial established that lung cancer mortality in specific high-risk groups can be reduced by annual screening with low-dose computed tomography. These findings indicate that the adoption of lung cancer screening could save many lives. Based on the results of the National Lung Screening Trial, the American Cancer Society is issuing an initial guideline for lung cancer screening. This guideline recommends that clinicians with access to high-volume, high-quality lung cancer screening and treatment centers should initiate a discussion about screening with apparently healthy patients aged 55 years to 74 years who have at least a 30-pack-year smoking history and who currently smoke or have quit within the past 15 years. A process of informed and shared decision making with a clinician related to the potential benefits, limitations, and harms associated with screening for lung cancer with low-dose computed tomography should occur before any decision is made to initiate lung cancer screening. Smoking cessation counseling remains a high priority for clinical attention in discussions with current smokers, who should be informed of their continuing risk of lung cancer. Screening should not be viewed as an alternative to smoking cessation."
(American Cancer Society: http://www.cancer.org/acs/groups/cid/documents/webcontent/acspc-039558-pdf.pdf))

"The American Cancer Society has thoroughly reviewed the subject of lung cancer screening and issued guidelines that are aimed at doctors and other health care providers:

Patients should be asked about their smoking history. Patients who meet ALL of the following criteria may be candidates for lung cancer screening:

- 55 to 74 years old
- In fairly good health (discussed further down)
- Have at least a 30 pack-year smoking history (Someone who smoked a pack of cigarettes per day for 30 years has a 30 pack-year smoking history, as does someone who smoked 2 packs a day for 10 years and then a pack a day for another 10 years.)
- Are either still smoking or have quit smoking within the last 15 years.

These criteria were based on what was used in the NLST.

Doctors should talk to these patients about the benefits, limitations, and potential harms of lung cancer screening. Screening should only be done at facilities that have the right type of CT scan and that have a great deal of experience in LDCT scans for lung cancer screening. The facility should also have a team of specialists that can provide the appropriate care and follow-up of patients with abnormal results on the scans.

Screening is meant to find cancer in people who do not have symptoms of the disease. People who already have symptoms that might be caused by lung cancer may need tests such as CT scans to find the underlying cause, which in some cases may be cancer. Still, this kind of testing is for diagnosis and is not the same as screening. Some of the possible symptoms of lung cancer that kept people out of the NLST were coughing up blood and weight loss without trying. To get the most potential benefit from screening, patients need to be in good health. For example, they need to be able to have surgery and other treatments to try to cure lung cancer if it is found. Patients who require home oxygen therapy most likely could not withstand having part of a lung removed, and so are not candidates for screening. Patients with other serious medical problems that would shorten their lives or keep them from having surgery may also not be able to benefit enough from screening for it to be worth the risks, and so should also not be screened. Metal implants in the chest (like pacemakers) or back (like rods in the spine) can interfere with x-rays and lead to poor quality CT images of the lungs. People with these types of implants were also kept out of the NLST, and so should not be screened with CT scans for lung cancer according to the ACS guidelines. People who have been treated for lung cancer often have follow-up tests, including CT scans to see if the cancer has come back or spread. This is called surveillance and is not the same as screening. (People with a prior history of lung cancer were not eligible for the NLST.)"

We note that the American College of Radiology commented on the American Cancer Society screening guidelines (described earlier).

"The American College of Radiology (ACR) acknowledges the importance of the new American Cancer Society recommendations for lung cancer screening using computed tomography (CT) scans. The ACR stresses that guidelines and practice standards are needed, and must be appropriately implemented, to ensure that patients nationwide have access to uniform, quality care and can expect a similar life-saving benefit from these exams as demonstrated in clinical trials.

Such guidelines must take into consideration the potential for false positives, incidental findings and other consequences that might negatively impact patients. The ACR is working on a practice guideline as well as ACR Appropriateness Criteria® based on thorough vetting of the peer reviewed literature."

'We continue to push forward in our work on standards regarding how and when these screening exams are conducted to help make sure that those who should be screened can do so regardless of where they live, but these standards need adequate time to be finalized to support a robust screening program that will provide the life-saving results that everyone wants,' said Paul Ellenbogen, MD, FACR, chair of the ACR Board of Chancellors."

The ACR supports the use of techniques shown to significantly reduce the number of people who die each year from lung cancer. Recent evidence, particularly results of the National Lung Cancer Screening Trial (NLST), has shown that CT lung cancer screening is appropriate when performed in the context of careful patient selection and follow-up.

However, barriers to widespread access to CT lung cancer screening remain — including acceptance of the cost-effectiveness of such a national screening program by Medicare and private insurers and associated coverage of these exams. While some insurers cover these exams, many may be waiting for the cost-effectiveness data from the NLST to be published later this year."

6. Modeling

de Koning HJ, Meza R, Plevritis SK, ten Haaf K, Munshi VN, Jeon J, Erdogan SA, Kong CY, Han SS, van Rosmalen J, Choi SE, Pinsky PF, Berrington de Gonzalez A, Berg CD, Black WC, Tammemägi MC, Hazelton WD, Feuer EJ, McMahon PM. Benefits and harms of computed tomography lung cancer screening strategies: a comparative modeling study for the U.S. Preventive Services Task Force. Ann Intern Med. 2014 Mar 4;160(5):311-20. doi: 10.7326/M13-2316. PMID: 24379002

de Koning and colleagues reported the results of simulation models of LDCT lung cancer screening scenarios "to estimate future harms and benefits of lung cancer screening and identify a set of possible efficient lung cancer screening policies by using 5 separately developed microsimulation models calibrated to the 2 largest randomized controlled trials on lung cancer screening." Five simulation models [Erasmus Medical Center in Rotterdam, the Netherlands (model E); Fred Hutchinson Cancer Research Center in Seattle, Washington (model F); the Massachusetts General Hospital in Boston, Massachusetts (model M); Stanford University in Stanford, California (model S); and the University of Michigan in Ann Arbor, Michigan (model U)] were calibrated according to the NLST and the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO). In all models, 100 % adherence was assumed.

The investigators reported: "The most advantageous strategy was annual screening from ages 55 through 80 years for ever smokers with a smoking history of at least 30 pack-years and ex-smokers with less than 15 years since quitting. It would lead to 50 % (model ranges, 45 % to 54 %) of cases of cancer being detected at an early stage (stage I/II), 575 screenings examinations per lung cancer death averted, a 14 % (range, 8.2 % to 23.5 %) reduction in lung cancer mortality, 497 lung cancer deaths averted, and 5250 life-years gained per the 100 000-member cohort. Harms would include 67 550 false-positive test results, 910 biopsies or surgeries for benign lesions, and 190 over diagnosed cases of cancer (3.7 % of all cases of lung cancer [model ranges, 1.4 % to 8.3 %])."

It is unclear why and how the PLCO (Oken, 2011), which evaluated chest x-ray screening, was used in model calibration. The simulation of LDCT screening appears to be based entirely on the NLST results and parameters since no other trial on LDCT was included. Sensitivity analysis of harms was specifically reported. Specific harms of follow-up were not listed.

7. Public Comments

The comments received on the proposed national coverage determination can be viewed in their entirety on the CMS Website at: http://www.cms.gov/medicare-coverage-database/details/nca-view-public-comments.aspx?NCAId=274.

During the initial 30-day comment period (2/10/2014 – 3/12/2014), CMS received 330 comments from various entities including providers, advocacy organizations, academic institutions, trade associations, and the general public. Of the comments received, 278 commenters advocated for coverage of lung cancer screening with LDCT, 27 supported coverage with conditions, 2 opposed, and 23 did not express a position.

During the 30-day comment period on the proposed NCD (11/10/2014 – 12/10/2014), CMS received 133 comments from various entities including professional medical societies, medical professionals and facilities, imaging centers, patient advocacy organizations, research consultants, device manufacturers, and the general public. Commenters were generally supportive of the proposed national coverage determination to expand Medicare coverage to include lung cancer screening as an additional preventive service.

A number of commenters supported coverage of lung cancer screening with LDCT noting that it is a positive step forward and provides for early detection of lung cancer in appropriate beneficiaries at high risk. Supportive commenters also believed that the proposed national coverage determination balances the risks, harms, and benefits of screening, while ensuring appropriate access to these services, and believed that lung cancer screening with LDCT requires careful implementation in centers of proven expertise in chest radiology, pulmonary thoracic surgery, and medical and radiation oncology, in a multidisciplinary and coordinated effort with registry management of findings and follow-up.

Some commenters expressed their support while also raising points for CMS to consider and suggested modifications to the proposed NCD. Some commenters did not express an opinion on the proposed NCD. Commenters addressed additional risk factors for lung cancer and conditions like asbestosis and radon exposure. A few commenters were opposed to coverage for these services, with some opining that if individuals choose to smoke that Medicare funds should not be used for screening and treatment of resulting conditions. Others suggested that Medicare should consider coverage for other screening modalities instead of lung cancer screening

with LDCT.

Commenters provided feedback on, and suggested modifications to, the proposed coverage requirements for beneficiaries, radiologists, and imaging centers. Our responses to the public comments are addressed below.

Beneficiary Eligibility Criteria

Comment:
Commenters suggested that CMS reassess the proposed age criteria of 55-74, specifically to expand coverage for beneficiaries up to age 80, with some commenters opining that the median age of diagnosis of 70 suggests that those older than 74 would also benefit from screening. Many commenters believed that the age criteria should align with the USPSTF recommendation, with a few commenters opining that CMS' proposed national coverage determination would violate the equal protection clause of the Fourteenth Amendment of the United States Constitution since private insurers cover preventive services consistent with USPSTF recommendations for these services. Some commenters recommended expanding coverage based on modeling studies. Other commenters suggested that a beneficiary's overall health status is a better indicator of how a beneficiary will handle cancer treatments rather than a specific age range and suggested eliminating the age criteria in its entirety.

Response:
We do not agree with the commenters that suggest that the proposed age range and coverage requirements violate the equal protection clause of the Fourteenth Amendment. By its terms, that amendment applies to States and not to the Federal government. Additionally, the statute governing "additional preventive services" for the Medicare program, §1861(ddd) of the Social Security Act, is not the same as the statute governing coverage of preventive health services for group health plans under 42 U.S.C. § 300gg-13. The statute governing coverage of preventive services for group health plans ensures coverage of certain immunizations and additional preventive services for infants, children, adolescents and women that are not included in title XVIII of the Social Security Act. The two statutes are not identical and the commenters are comparing two groups of patients who are not similarly situated.

Although it is true that both statutes recognize the importance of items and services that have received grade A or B recommendations by the USPSTF, the Medicare statute also enables the Secretary to consider whether the service is "reasonable and necessary for the prevention or early detection of an illness or disability" and "appropriate for individuals entitled to benefits under part A or enrolled in part B" before adding a new preventive service under part B. We believe that these two aspects of Section 1861(ddd) of the Social Security Act provide the authority to treat Medicare beneficiaries differently.

As discussed in the analysis, our age range was set using the enrollment age criteria of the NLST. As the study participants continued with the three annual screenings, benefit and harms data were recorded on participants up to and including the age of 77 years. Data on these patients were analyzed along with the other trial participants to demonstrate overall benefits. In the age specific analysis (Pinsky, 2014), no statistically significant increase in harms was reported. Therefore, we are modifying the beneficiary eligibility criteria to include beneficiaries 55 to 77 years of age.

There is no empirical data available for adults aged 78-80 years nor is there adequate evidence to cover LDCT screening for individuals beyond 55 – 77 years of age. Data from well-done randomized controlled trials provide the strongest evidence. We believe data from modeling is inadequate to ensure that the service would be "reasonable and necessary" or "appropriate" for Medicare beneficiaries, for purposes of §1861(ddd) of the Social Security Act.

Comment:
Several commenters requested that CMS modify the asymptomatic criterion. Commenters believed that to require the beneficiary show no signs or symptoms of lung disease would inappropriately limit coverage for this benefit. One commenter suggested allowing coverage for all beneficiaries, regardless of whether they had signs or symptoms of lung disease.

Response:
In response to the commenters' concerns, we are modifying this beneficiary eligibility criterion to state that a beneficiary must be "asymptomatic (no signs or symptoms of lung cancer)", consistent with the evidence reviewed and comments received.

Comment:
A few commenters suggested that Medicare cover NCCN Group 2 (ages 50-54, 20-pack year smoking history, and one additional risk factor for lung cancer) under coverage with evidence development. Commenters opined that individuals in NCCN Group 2 are equivalent to individuals that would fall under NCCN Group 1. Other commenters asked for expanded coverage to those who have quit smoking more than 15 years ago.

Response:
The NLST was the only trial (of several trials and observational studies over the past decade) to show benefits of lung cancer screening with LDCT. The NLST provided the evidence to determine that this service is "reasonable and necessary" and "appropriate" for Medicare beneficiaries. We did not find evidence of improvements in health outcomes in other populations, such as those suggested by the commenters (for instance, individuals that have a smoking cessation history greater than 15 years and individuals with a 20-pack year smoking history). We will continue to closely monitor ongoing trials, which we believe will improve the evidence base, and will consider modifying coverage in the future as appropriate.

Counseling and Shared Decision Making Visit/Written Orders

Comment:
Commenters generally supported the requirement that for the initial LDCT lung cancer screening, beneficiaries obtain a written order from a counseling and shared decision making visit. Others suggested that requiring a separate visit was difficult to incorporate into normal physician practice, and that mandating a face-to-face visit would limit access to screening services for beneficiaries in rural areas. One commenter questioned the need for the shared decision making visit if the written order was properly documented. Commenters also asked whether the counseling and shared decision making visit would be required for individuals that started lung cancer screening prior to becoming Medicare beneficiaries.

Response:
We believe that a counseling and shared decision making visit that addresses the benefits and harms of screening is supported by the evidence and is essential for ensuring that appropriate eligible beneficiaries receive these initial services with full knowledge of the risks, benefits, and commitment necessary to receive the most benefit from a lung cancer screening program. Among other things, there is the potential for significant harms in starting a lung cancer screening program, including the risk for false-positive results leading to additional tests and treatments that may be more harmful. The goal of shared decision making is not merely to furnish a written order for such services, but that both the practitioner and the beneficiary are armed with a better understanding of the relevant risk factors, and are engaged with shared responsibility regarding the decision to proceed or not proceed with a lung cancer screening program. We believe that the initial counseling and shared decision making visit supports identification of individuals that would most benefit from a lung cancer screening program.

Comment:
Commenters requested clarification about who could furnish the initial counseling and shared decision making visit, with others opining that nurses, psychologists, and imaging facilities should also be eligible to furnish these services.

Response:
We believe that formal shared decision making between the physician or qualified non-physician practitioner and the beneficiary is an important and essential component to an effective lung cancer screening program. We leave it to the discretion of the physician or qualified non-physician practitioner to determine whether other medical professionals should also participate in the visit based on a particular beneficiary's needs. Therefore, we are maintaining the requirement that the counseling and shared decision making visit must be furnished by a physician or qualified non-physician practitioner.

Comment:
A few commenters asked whether standardized instruments existed that could be used during the initial counseling and shared decision making visit and whether such instruments would need to be approved by CMS.

Response:
We understand that specific decision aids for lung cancer screening are being developed and will become more readily available as screening is more broadly adopted. While we are not requiring the use of a specific instrument, eligible practitioners may select from various available decision aids designed for this purpose and recognized by national professional medical organizations. For instance, the National Institutes of Health's National Cancer Institute has developed a decision aid/tool, available at: http://www.cancer.gov/newscenter/qa/2002/NLSTstudyGuidePatientsPhysicians.

Comment:
For subsequent screenings, some commenters disagreed with the requirement that the beneficiary must receive a written order. Other commenters requested clarification about how a written order for subsequent screenings should be obtained.

Response:
We agree that for subsequent screenings, a separate counseling and shared decision making visit (as required for the initial screening) would be overly burdensome. However, we believe that in order to balance the benefits, harms, and complex nature of this service, the beneficiary needs to obtain a written order for subsequent screenings to support continued shared decision making in light of the beneficiary's changing health status, particularly as one ages. For example, the Medicare-covered annual wellness visit (AWV) may be one option for obtaining such an order. The AWV includes elements for the furnishing of appropriate referrals and orders for preventive services.

Therefore, we are maintaining the criterion that a beneficiary must receive a written order for subsequent screenings during any appropriate visit with a physician or qualified non-physician practitioner. While we are not requiring a separate counseling and shared decision making visit for subsequent screenings, we are modifying this criterion to note that if a physician or qualified non-physician practitioner chooses to furnish a counseling and shared decision making visit for subsequent screenings, the visit must include all of the components required for an initial counseling and shared decision making visit as defined in this NCD.

Reading Radiologist Eligibility Criteria

Comment:
Commenters suggested that CMS modify the proposed requirements for radiologists eligible to perform lung cancer screening to add board eligibility in addition to proposed board certification. Another commenter suggested that CMS remove the requirement for board certification.

Response:
In response to the comments received, we are modifying the criterion to indicate that reading radiologists eligible to furnish these services must be board certified or board eligible with the American Board of Radiology or equivalent organization. These modifications are consistent with the evidence reviewed, including the NLST, where the reading radiologists were American Board of Radiology certified or board-eligible or had equivalent qualifications as defined by the American College of Radiology Practice Guidelines.

Radiology Imaging Facility Eligibility Criteria

Comment:
Commenters suggested modifications to the coverage requirements for radiology imaging facilities. Some commenters asked that CMS allow screening to be performed by an accredited provider of chest CT with training and experience in LDCT lung cancer screening. Other commenters requested clarification on how the criteria to be an advanced diagnostic imaging center would be met. One commenter requested that CMS use a professional medical society's lung cancer screening center certification program as a template for facility certification. Another commenter noted that all centers should meet the same eligibility requirements.

One commenter suggested that screening should only be covered in imaging facilities that participated in lung cancer screening trials since the commenter opined that the value of lung cancer screening varies markedly depending on how it is implemented. A few commenters were concerned that without quality requirements, patients could be at risk for over-exposure to radiation and/or have poor quality exams, resulting in additional harm and missed cancers. Other commenters suggested other facility types may be appropriate to perform these services, such as hospital imaging departments.

Commenters also opined that requiring past participation in the NLST or advanced diagnostic imaging center accreditation with training and experience in LDCT lung cancer screening would place an undue burden on patients and rural facilities. Some commenters recommended that CMS acknowledge professional society accreditation or participation in other studies besides the NLST for purposes of meeting the eligibility criteria, while also ensuring quality standards.

Response:
We appreciate the commenters' extensive feedback regarding the proposed imaging facility eligibility criteria. While we agree with some of the commenters that requiring past participation in the NLST or advanced diagnostic imaging center accreditation with experience in LDCT lung cancer screening would place an undue burden on imaging facilities, we also agree with the commenters who expressed concern that without quality requirements, beneficiaries could be exposed to additional harms. Included in CMS' review of the evidence were evidence-based recommendations on the necessary components of a high quality lung cancer screening program. As reported by Mazzone and colleagues (2014), necessary components include, among other things, the establishment of a lung nodule identification, classification, and reporting system; and integration of smoking cessation interventions into a lung cancer screening program.

Based on the evidence reviewed, including the public comments received, and to ensure appropriate access to these services, we are modifying the imaging facility eligibility criteria by removing the requirement for either past participation in lung cancer screening trials or advanced diagnostic imaging accreditation with training and experience in LDCT lung cancer screening. We are requiring that imaging facilities utilize standardized lung nodule identification, classification, and reporting systems, and make available smoking cessation interventions for current smokers, based on the evidence reviewed. We believe these modifications strike an appropriate balance between maintaining appropriate and high quality access to these services, while reducing burden.

Comment:
Regarding the effective radiation dose, commenters suggested various technical revisions including that the radiation dose should be as low as possible, and that CMS should allow for adjustments based on the size of the individual. Some commenters opined that milligray (mGy) is a more common measurement than millisievert (mSv) for expressing volumetric dose.

Response:
We are revising the imaging facility eligibility criteria in light of the public comments. The proposed radiation dose was developed to align with the NLST. The NLST research team (2011) reported that the acquisition variables were chosen to reduce exposure to an average effective dose of 1.5 mSv." Based on the comments received and the evidence reviewed (including recently published evidence-based multi-society, multi-disciplinary professional guidelines), we are modifying the imaging facility criteria to state that an eligible facility must be one that performs LDCT with volumetric CT dose index (CTDIvol) of ≤ 3.0 mGy (milligray) for standard size patients (defined to be 5' 7" tall; and approximately 155 pounds) with appropriate reductions in CTDIvol for smaller patients and appropriate increases in CTDIvol for larger patients.

Registry Requirements and Data Elements

Comment:
Some commenters expressed concern about the feasibility of tracking and submitting registry data related to diagnostic follow-up, cancer incidence, and lung-cancer/all-cause mortality. Commenters were concerned that tracking diagnostic procedures and outcomes may be logistically difficult since diagnostic follow-up may not necessarily be carried out at the center performing the LDCT screening. A few commenters suggested that a registry is not needed for these services and would limit access to screening (particularly in small, non-academic facilities). Others indicated that the number of data elements proposed is overly burdensome. Commenters' suggested alternatives included limiting registry data elements to those items that could be ascertained at the time of the screen or shortly thereafter (screening results). Some commenters suggested adding additional data elements to the registry that capture other risks for lung cancer. One commenter suggested that CMS review and reference current consensus guidelines from various professional societies as a reporting mechanism. One commenter requested information about existing registries that would meet CMS requirements, while another asked for clarification about the objectives, planned uses of the registry data, requirements for registry administration, and CMS solicitation and approval of registries.

Response:
The primary purpose for requiring the submission of data to the registry is to document compliance with the coverage criteria that are not evidenced on the health care claim. Furthermore, based on the public comments and the evidence reviewed, we strongly believe that the registry will serve as an aid to those seeking to study the clinical benefits of this screening. The registry and the other criteria required in this NCD are supported by the evidence reviewed, including the NLST. The registry will help ensure that only eligible beneficiaries will receive this screening service since only beneficiaries that meet the eligibility requirements will benefit from such screening.

Furthermore, we recognize the impact of this criterion for imaging facilities. We will only require production of the minimum number of data elements to carry out this payment function in an effort to reduce burdens. Therefore, we are modifying the data registry elements, based on our review of the evidence and feedback received from commenters. As amended, the data elements are limited to those required to determine whether an individual has met the coverage criteria for the LDCT lung cancer screening service, that is, whether their receipt of the service was "reasonable and necessary" and "appropriate." Data collected and submitted to a CMS-approved national registry must include, at minimum, all of the following elements:

Data Type	***Minimum Required Data Elements***
Facility	Identifier
Radiologist (reading)	National Provider Identifier (NPI)
Patient	Identifier
Ordering Practitioner	National Provider Identifier (NPI)
CT scanner	Manufacturer, Model
Indication	Lung cancer LDCT screening – absence of signs or symptoms of lung cancer

Data Type	*Minimum Required Data Elements*
System	Lung nodule identification, classification and reporting system
Smoking history	Current status (current, former, never), If former smoker, years since quitting, Pack-years as reported by the ordering practitioner, For current smokers, smoking cessation interventions available.
Effective radiation dose	CT Dose Index (CTDIvol)
Screening	Screen date Initial Screen or Subsequent Screen

Additionally, national registries are strongly encouraged to collect data on lung nodules (for example: clinically significant non-lung cancer findings, the number and types of nodules, and size and location of each nodule), subsequent diagnostic testing, adverse events, and intermediate and long term health outcomes, in order to inform practices and policymakers about the ability to implement a LDCT lung cancer screening program broadly in multiple settings across the country, and achieve positive outcomes, consistent with the NLST. We recognize that these other data elements are extremely important to establishing the benefit of these screening services and improvement in health outcomes. We strongly encourage submission of such data elements to registries in addition to the minimum elements required under this NCD. These data will not only verify that screening leads to improved health outcomes for the Medicare population, but will also serve as the basis to refine and improve screening in practice, and serve the quality improvement purposes of screening facilities. We believe that multi-society stakeholders are in the best position to determine the appropriate data elements for reaching these goals, and to adjust the particular elements over time.

All CMS-approved registries must have the capacity and capability to collect data from any Medicare-eligible imaging facility/department that furnishes lung cancer screening with LDCT, with a catchment area that includes all 50 States, United States Territories, and the District of Columbia. CMS will evaluate each entity interested in participating as a CMS-approved registry to determine if they are capable of meeting the registry and data collection requirements outlined in this national coverage determination, including:

a. Establishment of a steering committee and a governance board for oversight of the registry;
b. Registry management plan, including identification of key personnel;
c. Operational plan and framework that describes mechanisms for collection and submission of data from imaging facilities to the registry;
d. Registry catchment area;

e. Mechanisms for the submission of registry data to CMS electronically;
f. Mechanisms to collect information (e.g.; HICN) in order to permit linkage of registry data with external databases (e.g. Medicare claims data sets);
g. Description of data management and data quality review methods, including validation;
h. Use of CMS-approved standardized data dictionary;
i. Mechanisms for submitting a list of facilities participating in the registry to CMS; and
j. Quality assurance plan.

To apply to function as a CMS-approved registry, interested entities must submit a letter of interest along with detailed supporting information about how the interested entity is able to meet the requirements outlined in this national coverage determination to the following address or via email to caginquiries@cms.hhs.gov.

Centers for Medicare & Medicaid Services
Center for Clinical Standards and Quality
Director, Coverage and Analysis Group
ATTN: Lung Cancer LDCT Screening
Mail Stop: S3-02-01
7500 Security Blvd.
Baltimore, MD 21244

Information regarding CMS-approved registries will be posted on the CMS website.

Additional Comments

Comment:
One commenter asked that CMS ensure that lung cancer screening is performed as a part of a dedicated, multi-disciplinary program to image, diagnose and manage high risk patients and opined that lung cancer screening is only one part of the paradigm of management of high risk patients in order to achieve positive results with lung cancer screening.

Response:
We have set coverage criteria to implement lung cancer screening with LDCT in a responsible manner as part of a lung cancer screening program, in order to ensure positive outcomes of this screening service in the Medicare population. These coverage criteria are consistent with the evidence reviewed including the NLST and information about "implementation of a lung cancer screening program" from the USPSTF (Moyer 2014).

Comment:
One commenter expressed concern about possible over-diagnosis of lung cancer in the screened population and the effect that screening would have on post-lobectomy survival rates.

Response:
We appreciate these commenters' concerns. They also reflect the concerns raised by the MEDCAC. We acknowledge that there is the potential for significant harms in starting a lung cancer screening program, including the risk for false-positive results leading to additional tests and treatments that may be more harmful. There are potential benefits of lung cancer screening with LDCT if implemented carefully. We are establishing specific beneficiary, provider and imaging facility eligibility requirements, along with inclusion of a counseling and shared decision making visit to ensure that the benefits of screening outweigh harms for the Medicare population.

Comment:
A few commenters were opposed to Medicare coverage of lung cancer screening with LDCT, with some commenters suggesting that other screening methods, such as breath tests, should be considered for coverage instead of lung cancer screening with LDCT. A few commenters believe that Medicare funds should not be used for lung cancer screening in individuals who have chosen to smoke. A few commenters asked about other risk factors for lung cancer such as radon or asbestos exposure.

Response:
We appreciate the commenters' concerns since lung cancer is the leading cause of cancer deaths in the United States. At this time, there are no other proven screening tests. The USPSTF grade B recommendation was limited to patients with a history of smoking and the evidence in the NLST focused on heavy smoking. Therefore, we consider these suggestions to be outside the scope of this national coverage analysis. In order to consider adding screening for lung cancer for additional indications or conditions, there would need to be a specific recommendation from the USPSTF along with evidence concerning the other factors identified in §1861(ddd) of the Social Security Act and regulations at 42 C.F.R. § 410.64.

We believe that this national coverage determination implements lung cancer screening with LDCT in a responsible manner. CMS will continue to monitor the evidence as stewards of the Medicare program. We strongly encourage Medicare beneficiaries to stop smoking since smoking is a major risk factor for development of lung cancer.

Comment:
A few commenters requested information about coding, reimbursement, and Medicare-covered tobacco cessation counseling services.

Response:
While coding and reimbursement are outside the scope of this national coverage analysis, we plan to develop appropriate educational materials, including a Medicare Learning Network article. Information regarding Medicare coverage of tobacco cessation counseling services can be found in Pub. 100-03, Medicare National Coverage Determinations Manual, Chapter 1, Sections 210.4 and 210.4.1.

Comment:
One commenter believed that CMS did not have authority to designate eligibility criteria for facilities and radiologists because medical licensure is determined by State governments.

Response:
While we agree that medical licensure is primarily a State responsibility, Congress has frequently established specific conditions of coverage or payment for particular services under the Medicare program. Congress has expressly authorized CMS to add coverage for additional preventive services under certain conditions as set forth in §1861(ddd) of the Act, when those services are found to be appropriate for individuals entitled to benefits under part A or enrolled under part B, as determined via the NCD process. As part of this appropriateness determination, it is reasonable to consider the qualification of the radiologists and facilities that may be furnishing this new service. It would be difficult, if not impossible, to expand coverage for a new preventive service without addressing the qualifications of the providers and suppliers who are to be paid for furnishing this care under a national program.

We are finalizing eligibility criteria for radiologists and imaging facilities for lung cancer screening with modifications based on the evidence reviewed, including public comments, in light of some of the added risks of this particular procedure (for example, exposure to radiation even at low doses creates a patient safety concern). Using the NCD process, we have asked for and received public comments about those criteria. We have made some changes to those criteria as a result of the public comments. We believe our actions are consistent with our authority under the Medicare statute and do not interfere with State licensing determinations.

VIII. Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act (§ 1869(f)(1)(B)). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Since January 1, 2009, CMS is authorized to cover "additional preventive services" (see Section III above) if certain statutory requirements are met as provided under § 1861(ddd) of the Social Security Act. Regulations at 42 C.F.R. § 410.64 provide:

(a) Medicare Part B pays for additional preventive services not described in paragraph (1) or (3) of the definition of "preventive services" under §410.2, that identify medical conditions or risk factors for individuals if the Secretary determines through the national coverage determination process (as defined in section 1869(f)(1)(B) of the Act) that these services are all of the following:

(1) Reasonable and necessary for the prevention or early detection of illness or disability.
(2) Recommended with a grade of A or B by the United States Preventive Services Task Force.
(3) Appropriate for individuals entitled to benefits under part A or enrolled under Part B.

(b) In making determinations under paragraph (a) of this section regarding the coverage of a new preventive service, the Secretary may conduct an assessment of the relation between predicted outcomes and the expenditures for such services and may take into account the results of such an assessment in making such national coverage determinations.

Question 1: Is the evidence sufficient to determine that screening for lung cancer with low dose computed tomography is recommended with a grade of A or B by the United States Preventive Services Task Force?

In 2014, Moyer and colleagues, on behalf of the USPSTF, reported: "The USPSTF recommends annual screening for lung cancer with low-dose computed tomography in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery. (B recommendation)" (Moyer, 2014). The evidence is sufficient to conclude that lung cancer screening with LDCT is recommended with a grade B by the USPSTF.

Prior to the current recommendation, the USPSTF evaluated lung cancer screening in 1996 (grade D) and in 2004 (grade I – consistent with current I statement) based upon 6 observational studies (Humphrey, 2004). The change in recommendation was based upon four trials (DANTE, DLSCT, MILD, NLST) (Humphrey, 2011). Net benefit of screening was supported primarily by the NLST (for individuals aged 55 to 74 years who have ≥ 30 pack-year smoking histories and current smokers or have quit in the past 15 years). Extension of the upper age beyond NLST data was based upon modeling only, with no empirical data.

In the 2014 considerations, the USPSTF specifically noted recommendations for:

"Implementation of a Lung Cancer Screening Program

Screening Eligibility, Screening Intervals, and Starting and Stopping Ages

The NLST, the largest RCT to date with more than 50,000 patients, enrolled participants aged 55 to 74 years at the time of randomization who had a tobacco use history of at least 30 pack-years and were current smokers or had quit within the past 15 years. The USPSTF recommends extending the program used in the NLST through age 80 years. Screening should be discontinued once the person has not smoked for 15 years.

The NLST enrolled generally healthy persons, and the findings may not accurately reflect the balance of benefits and harms in those with comorbid conditions. The USPSTF recommends discontinuing screening if a person develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery.

Clinicians will encounter patients who are interested in screening but do not meet the criteria of high risk for lung cancer as described previously. The balance of benefits and harms of screening may be unfavorable in these lower-risk patients. Current evidence is lacking on the net benefit of expanding LDCT screening to include lower-risk patients. It is important that persons who are at lower risk for lung cancer be aware of the potential harms of screening. Future improvements in risk assessment tools will help clinicians better individualize patients' risks.

Smoking Cessation Counseling

All persons enrolled in a screening program should receive smoking cessation interventions. To be consistent with the USPSTF recommendation on counseling and interventions to prevent tobacco use and tobacco-caused disease, persons who are referred to a lung cancer screening program through primary care should receive these interventions before referral. Because many persons may enter screening through pathways besides referral from primary care, the USPSTF encourages incorporating such interventions into the screening program.

Shared Decision Making

Shared decision making is important for persons within the population for whom screening is recommended. The benefit of screening varies with risk because persons who are at higher risk because of smoking history or other risk factors are more likely to benefit. Screening cannot prevent most lung cancer deaths, and smoking cessation remains essential. Lung cancer screening has substantial harms, most notably the risk for false-positive results and incidental findings that lead to a cascade of testing and treatment that may result in more harms, including the anxiety of living with a lesion that may be cancer. Overdiagnosis of lung cancer and the risks of radiation are real harms, although their magnitude is uncertain. The decision to begin screening should be the result of a

thorough discussion of the possible benefits, limitations, and known and uncertain harms.

Standardization of LDCT Screening and Follow-Up of Abnormal Findings

The evidence for the effectiveness of screening for lung cancer with LDCT comes from RCTs done in large academic medical centers with expertise in using LDCT and diagnosing and managing abnormal lung lesions. Clinical settings that have high rates of diagnostic accuracy using LDCT, appropriate follow-up protocols for positive results, and clear criteria for doing invasive procedures are more likely to duplicate the results found in trials. The USPSTF supports adherence to quality standards for LDCT and establishing protocols to follow up abnormal results, such as those proposed by the National Comprehensive Cancer Network (NCCN). A mechanism should be implemented to ensure adherence to these standards.

In the context of substantial uncertainty about how best to manage individual lesions, as well as the magnitude of some of the harms of screening, the USPSTF encourages the development of a registry to ensure that appropriate data are collected from screening programs to foster continuous improvement over time. The registry should also compile data on incidental findings and the testing and interventions that occur as a result of these findings."

Question 2: Is the evidence sufficient to determine that screening for lung cancer with low dose computed tomography is reasonable and necessary for the prevention or early detection of illness or disability?

Since 2004, four trials (DANTE, DLSCT, MILD, NLST) evaluated lung cancer screening using LDCT. One large trial (NLST, 2011; n = 53,454) showed three annual LDCT screenings of individuals aged 55 to 74 years, who have ≥ 30 pack-year smoking history, and are current smokers or have quit in the past 15 years, reduced lung cancer mortality. Two smaller trials (DANTE, 2009, n = 2472; DLSCT, 2012, n = 4104) did not find a significant difference in lung cancer mortality between LDCT screening compared to control (no screening). One trial compared annual to biennial screening and found no significant difference in lung cancer mortality (MILD, 2012, n = 4099).

The NLST is the only trial to demonstrate benefit of lung cancer screening with LDCT. It was a well conducted, large multicenter trial performed at 33 centers with trained and approved radiologists and follow-up evaluation at experienced centers. Investigators noted: "the NLST was conducted at a variety of medical institutions, many of which are recognized for their expertise in radiology and in the diagnosis and treatment of cancer. It is possible that community facilities will be less prepared to undertake screening programs and the medical care that must be associated with them."

DANTE and DLSCT evaluated participants who were similar in age of those studied in the NLST, but had a smaller smoking history ≥ 20 pack-year and compared to no screening. The MILD trial had methodologic issues which reduced study quality in comparison to the other included trials. In past trials, the benefits, mainly in lung cancer mortality, have been difficult to demonstrate due to a number of potential factors including patient selection, along with diagnosis and treatment following positive findings.

The NLST demonstrated benefit by enrolling a large number of high exposure patients (smoking history) to be followed for several years to detect a significant decrease (247 deaths from lung cancer per 100,000 person-years in the low-dose CT group and 309 deaths per 100,000 person-years in the radiography group; number needed to screen (NNS) to prevent one lung cancer death = 320). The trial was ended early after an interim analysis. The decision to compare to screening with chest radiology (Church, 1990) was made before the PLCO trial was completed that showed chest radiology did not reduce lung cancer mortality (Oken, 2011); however, the radiology group was exposed to harms that may not have occurred in a no screening control, potentially enhancing the relative benefits and the likelihood of a positive trial result. The harms of LDCT relate to the CT scan itself and the follow-up diagnostic tests or interventions (adverse events from bronchoscopies and biopsies), and patient psychosocial consequences, and have been recognized for many years as noted in past USPSTF reviews. For example, death within 60 days after most invasive diagnostic procedures was twice as high in the radiology group compared to the LDCT group (2.1 % versus 1.0 %; NLST, 2011), which with a large sample size may result in a meaningful difference. NLST investigators wrote: "one of the most important factors determining the success of screening will be the mortality associated with surgical resection, which was much lower in the NLST than has been reported previously in the general U.S. population (1 % vs. 4 %)." If this is not maintained with broad implementation of screening, the screening benefits may not be realized. A better understanding of why patients screened with LDCT had lower mortality from invasive procedures is needed. Questions such as whether the state of disease, patient, physician, or bias of either the physician/practitioner or patient may need to be considered.

While age inclusion criteria were comparable among trials, the majority of participants were in the 50-64 year age range. In the NLST, 26.6 percent (7110/26,722) of the individuals in the LDCT screening group were 65 years of age or older. Pinsky et al. (2014) noted: "NLST participants aged 65 years or older had a higher rate of false-positive screening results than those younger than 65 years by a higher cancer prevalence and PPV" [positive predictive value].

The NLST enrolled patients aged 55 to 74 and followed each of these participants at least 3 years. Therefore, we have data up to age 77 for some participants that entered the NLST at age 74. We had proposed an age range based on the NLST inclusion criteria but will extend the upper age to 77 years based on actual trial data. There are no trial data or evidence on adults over 77 years. Modeling was used to extend the age limit for the USPSTF recommendation. However, results from modeling vary widely based on the assumptions used in the modeling. de Koning et al. specifically reported that "models assumed 100 % adherence with screening," an unrealistic long term assumption for real world screening that even the NLST could not achieve (95 % adherence with three annual screens in LDCT group of NLST). The authors also noted that "extrapolations beyond those trials' [NLST, PLCO] time horizons, screening intervals, and eligibility criteria introduce uncertainty" (de Koning, 2014). It is difficult to interpret modeling of benefits and harms since models may be limited in consideration of older patients if inputs are based solely on data from younger populations. Patz et al. (2014) noted: "[a]s with any model, one should be cautious in extrapolating much beyond the data on which the model was based, which in this case are 3 annual screens and a total of approximately 7 years of follow-up."

It is recognized that the number and severity of comorbidities increases with age (Medicare Current Beneficiary Survey, 2011). Comorbidities may then influence the ability to tolerate invasive diagnostic procedures (e.g., risk for adverse events from bronchoscopy; Hehn, 2003) and may reduce the response of cancer treatments in older adults with multiple comorbidities. Wang and colleagues (2012) noted: "[c]omorbidity can have an impact on care for patients with NSCLC [non–small-cell lung cancer] in a variety of ways. First, patients with comorbidity are more likely to experience treatment toxicity, and treatments may exacerbate underlying comorbidity. Second, comorbidity decreases the likelihood of completing treatment. In a large trial (Frasci et al., 2000) patients with advanced NSCLC who had Charlson comorbidity index (CCI) scores ≥ 2 were more likely to discontinue chemotherapy. Third, significant comorbidities can limit life expectancy, particularly in earlier-stage cancers, decreasing the potential survival benefit of cancer treatment." Given these concerns without actual trial data to show that the benefits outweigh the harms, and the harms (e.g., mortality and morbidity from invasive procedures as biopsies) may be significant, the evidence is insufficient to determine that screening is reasonable and necessary for beneficiaries 78 years of age and older.

Smoking history is an important variable to consider since higher exposure increases risk; however, it is a difficult variable to accurately ascertain in general clinical practice due to recall or approximations since it is typically self-reported. A specific formal determination of smoking history is needed. Lung cancer screening outcomes may very well hinge on the initial determination. The NLST included individuals with ≥ 30 pack-year (mean = 56) smoking history while DANTE and DLSCT enrolled individuals with ≥ 20 pack-year smoking history. Over-diagnosis, the detection of indolent tumors that otherwise may not cause clinical symptoms ["more than 18 % of all lung cancers detected by LDCT in the NLST seem to be indolent" (Patz, 2014)], also influences the balance of benefits and harms of screening. The false positive rate of LDCT positive screens was very high in all three trials (DANTE, DLSCT, and NLST).

	Age (inclusion criterion)	**Smoking history (inclusion criterion)**	**Positive result LDCT (false positive rate)**
DANTE; n = 2472 (Infante, 2009)	mean age = 64.6; (60-74 years)	mean = 47 pack-years; (≥ 20 pack-years)	non-calcified nodule ≥ 10 mm, etc; (291/351, 83%)
DLSCT; n = 4104 (Saghir, 2012)	91% 50-64 years; (50-70 years)	mean = 36 pack-years; (≥ 20 pack-years)	nodule ≥ 5 mm; (542/611, 89%)
NLST; n = 53454 (NLST, 2011)	73% 55-64 years; (55-74 years)	mean = 56 pack-years; (≥ 30 pack-years)	non-calcified nodule ≥ 4 mm; (17497/18146, 96 %)

While progress has been made in limiting harms, especially radiation exposure, per screening scan, which was limited to an average of 1.5 mSv in the NLST, many individuals have follow-up chest CTs (LDCT or standard diagnostic CT in 49.8 percent in NLST LDCT group) or PET-CT scans (8.3 percent in NLST LDCT group; radiation dose of typical PET is greater than or equal to standard diagnostic CT). Accordingly, the low dose designation may be misleading in the sense that it may not reflect the total radiation exposure from screening for some

individuals.

Women comprised 45 percent of the study population in DLSCT and 41 percent in NLST. Gender was borderline as an interaction in NLST (p = 0.08; Pinsky, 2013). DANTE enrolled only men but gender alone is unlikely to account for all of the observed differences between the trials. Other patient and provider characteristics, nodule size and evaluation, sample size and control group interventions were likely factors. The high LDCT screening false positive rate for lung cancer in these trials and the subsequent need for follow-up of small lesions are concerning. It is difficult to estimate the full extent that additional testing at community centers, and the false positive rate, will have in the Medicare population, along with the potential harms of subsequent evaluation in beneficiaries with advanced age and comorbidities.

Overall, based primarily on the results of the NLST, we find that the evidence is sufficient to determine that screening for lung cancer with LDCT is reasonable and necessary for the prevention or early detection of illness or disability for the exact population studied in the NLST. This recommended screening population is consistent with recommendations and guidelines from major organizations such as the American Cancer Society, American Lung Association, and the American College of Chest Physicians. The American College of Radiology recommends the broader group, similar to the USPSTF recommendation while the American Academy of Family Physicians found insufficient evidence to recommend for or against screening.

There are substantial concerns that the benefits demonstrated in NLST may not be replicated with broad screening in the Medicare population. The National Cancer Institute which sponsored the NLST noted: "Questions will still remain about whether the balance of benefits and harms found in a study conducted by centres that have strong expertise in screening can be maintained in less regulated and less quality-controlled settings in the general community" (Kramer, 2011). While recognizing the importance of the NLST, the MEDCAC reinforced these concerns according to the committee's low confidence (2.22 out of 5 scale) that the benefits outweigh the harms of lung cancer screening with LDCT in the Medicare population (http://www.cms.gov/medicare-coverage-database/details/medcac-meeting-details.aspx?MEDCACId=68)

Marshall et al. (2013) noted: "[g]eneralization of findings from tightly controlled trial situations to large-scale mass screening programs require uniform standards and high quality control in order to be able to accurately track and assess nodules over time. Lung cancer screening is more than simple provision of a CT service; it is as a long-term commitment requiring extensive infrastructure to allow for invitation and recruitment; quality improvement; workforce/facility capacity for screening, diagnosis and treatment; health professional training; participant information and support. On-going evaluation and monitoring of the program is essential to ensure high standards of care are met and delivered in a consistent and acceptable way."

Comments submitted to the USPSTF expressed similar concerns. The USPSTF responded by adding a section on implementation "emphasizing the need for monitoring this implementation, quality assurance in diagnostic imaging, and appropriate follow-up to replicate the benefits observed in the NLST in the general population." This programmatic approach and implementation framework provide the foundation for our decision and enables LDCT lung cancer screening to be reasonable and necessary.

Since the NLST was the only trial of several trials and observational studies over the past decade to show benefits, there is no evidence of improvements in health outcomes from lung cancer screening using LDCT in other populations. The results of ongoing trials in Europe will help solidify the evidence base (Field, 2013). There is no evidence on LDCT lung cancer screening in adults over 75 years of age since no trial has included this subgroup. There is no evidence on screening with more than 3 annual LDCT scans. While modeling, if performed properly with evidence based assumptions, may generate interesting hypotheses, direct evidence from actual studies designed to test hypotheses are still needed. Sox (2014) recently wrote: "No one wants to repeat the experience with prostate cancer screening, which became a de facto standard of practice long before evidence from randomized trials signaled caution. The era of lung cancer screening begins with randomized trial evidence, but the potential for uncontrolled growth – and net harm – remains. If Medicare covers lung cancer screening, it must require routine reporting of recruitment, screening, diagnosis, and treatment of lung cancer from every screening site. The findings will help patients decide about screening, set benchmarks for evaluating programs, and inform policy about screening." The Veterans Health Administration is also implementing screening with data collection which will help "assess whether the predominantly older, male VHA population with several chronic conditions has different outcomes with screening from those of the younger, healthier NLST population" (Kinsinger, 2014).

With concerns and limitations, we find that the evidence is sufficient to conclude that lung cancer screening is reasonable and necessary for prevention or early detection of illness or disability, for Medicare beneficiaries under constraints similar to the NLST protocol, with specific eligibility requirements, performed by radiologists with specific LDCT training, and performed at qualified centers where specific data are collected. We note that LDCT screening has never been tested broadly in community settings or implemented on a widespread scale. Consistent with the USPSTF grade B recommendation, this programmatic approach and implementation framework allows LDCT lung cancer screening to be reasonable and necessary for Medicare beneficiaries. This approach was supported by evidence-based guidelines developed by multi-society multi-disciplinary stakeholders (Mazzone, 2014), and the two requestors of this national coverage determination. During the second comment period we received 133 comments, of which a large majority supported the framework of our proposed national coverage determination. Specific coverage criteria and other requirements have been adjusted accordingly in this final national coverage determination based on the evidence reviewed, including clarifications of published data and professional medical society position statements.

Question 3: Is the evidence sufficient to determine that screening for lung cancer with low dose computed tomography is appropriate for Medicare beneficiaries?

Lung cancer is a burdensome condition for the Medicare population due to the advanced stage and age at diagnosis and at death. Early detection with various screening tests has been studied for many years without positive results until the NLST. Based on the results of the NLST, lung cancer screening using LDCT was shown to reduce lung cancer mortality compared to screening with chest radiogram (x-ray) for a very defined screening population including a portion of the Medicare population. Since no other lung cancer screening test has been proven, there is no gold standard comparator to calculate sensitivity or specificity. Autopsy studies have not been published but may provide additional information in the future. The LDCT scan is relatively simple and attempts to balance radiation exposure to acceptable image quality, compared to standard diagnostic chest CT scans that are not appropriate for screening.

Medicare Beneficiary Eligibility

As noted above, the positive evidence for lung cancer screening with LDCT is from the NLST, with inclusion criteria limited to individuals aged 55 to 74 years who have ≥ 30 pack-year smoking history and currently smoke or have quit smoking within the past 15 years. Many commenters asked for a reassessment of the age range for screening. Our proposed age range was set to match the enrollment age criterion of NLST. As these participants continued with the three annual screenings, however, benefit and harms data were actually recorded on participants up to and including the age of 77 years. In age specific analysis (Pinsky, 2014), no statistically significant increase in harms was reported. Data on these patients were analyzed along with the other trial participants to demonstrate overall benefits. Actual data from a well conducted randomized controlled trial provides the strongest form of evidence. From the NLST, CMS finds sufficient evidence to support an expansion of appropriate LDCT screening for eligible beneficiaries 55 to 77 years of age. There are no data and no evidence to show improvements in health outcomes or that benefits outweigh harms, in smokers 78 years and older. Uncertain results from modeling based on unrealistic assumptions are insufficient.

Based on the evidence from the NLST, lung cancer screening with LDCT is only appropriate for Medicare beneficiaries as defined by the NLST and provided in a screening program.

Smoking History and Pack-Year Calculation

Smoking history is an important criterion for lung cancer screening using LDCT but is subject to recall bias (Bernaards, 2001; Krall, 1989; Mant, 2000; Persson, 1989; Prignot, 1987). Providers must ascertain smoking history accurately, taking into consideration intermittent periods of not smoking or reduced amounts, to ensure optimal screening outcomes.

One pack-year is equal to one pack of 20 cigarettes smoked each and every day for one year (Prignot, 1987).

Counseling and Shared Decision Making

Lung cancer screening with LDCT is a complex topic as noted above. Additionally, as discussed by Mazzone and colleages (2014) regarding who is offered lung cancer screening: "The principal question is how do lung cancer

screening programs identify a group at high enough risk of developing lung cancer to benefit more than they are harmed. The balance with this choice is that more lives can be saved by screening at lower thresholds of risk, but the relative harms of screening increase as the threshold is lowered. It is difficult to determine the ideal balance of benefit and harm as the value of the benefit and harms is not equal, and varies with patient preferences." Due to the complex factors involved in deciding whether to start a lung cancer screening program, formal shared decision making between the physician or non-physician practitioner and beneficiary is important. Eligible beneficiaries should be aware of, among other things, the individual commitment needed to gain benefits from a lung cancer screening program.

Barry and Edgman-Levitan (2012) noted: "[t]he process by which the optimal decision may be reached for a patient at a fateful health crossroads is called shared decision making and involves, at minimum, a clinician and the patient, although other members of the health care team or friends and family members may be invited to participate. In shared decision making, both parties share information: the clinician offers options and describes their risks and benefits, and the patient expresses his or her preferences and values. Each participant is thus armed with a better understanding of the relevant factors and shares responsibility in the decision about how to proceed. (Charles, 1997)"

Due to the specific patient selection criteria, benefits, harms, and adherence, along with the need for shared decision making, we believe that the lung cancer LDCT screening benefit should include a specific counseling and shared decision making visit that addresses the following:

1. Determination of beneficiary eligibility including age, absence of signs or symptoms of lung cancer, a specific calculation of cigarette smoking pack-years; if former smoker, the number of years since quitting;
2. Shared decision making, including the use of one or more decision aids, to include the benefits and harms of screening, including follow-up diagnostic testing, over-diagnosis, false positive rate, and total radiation exposure;
3. Counseling on the importance of adherence to annual lung cancer LDCT screening, impact of comorbidities and ability or willingness to undergo diagnosis and treatment;
4. Counseling on the importance of maintaining cigarette smoking abstinence if former smoker, or beginning/continuing tobacco use cessation if current smoker, and furnishing of information about tobacco cessation interventions.
5. If appropriate, the furnishing of a written order for lung cancer screening with LDCT that includes: the beneficiary's date of birth; current smoking status, actual pack-year smoking history (number); if former smoker, the number of years since quitting smoking; a statement that the beneficiary is asymptomatic (no signs or symptoms of lung cancer); and NPI of the ordering practitioner.

Decision aids may assist in this process. In a Cochrane Review, Stacey et al., noted "[a]ccording to the International Patient Decision Aids Standards (IPDAS) Collaboration, decision aids are evidence-based tools designed to help patients to participate in making specific and deliberated choices among healthcare options. Patient decision aids supplement (rather than replace) clinicians' counselling about options. The specific aims of decision aids and the type of decision support they provide may vary slightly, but in general they:

1. Explicitly state the decision that needs to be considered;
2. Provide evidence-based information about a health condition, the options, associated benefits, harms, probabilities, and scientific uncertainties;

3. Help patients to recognize the values-sensitive nature of the decision and to clarify, either implicitly or explicitly, the value they place on the benefits, harms, and scientific uncertainties. (To accomplish this, patient decision aids may describe the options in enough detail that clients can imagine what it is like to experience the physical, emotional, and social effects and/or guide clients to consider which benefits and harms are most important to them)."

As part of the counseling and shared decision making visit, we are requiring that, among other things, shared decision making (including the use of one or more decision aids) includes information on benefits, harms, follow-up diagnostic testing, over-diagnosis, false positive rate and total radiation exposure. We believe that specific decision aids for lung cancer screening are being developed and will become more readily available as screening is more broadly adopted. While we are not requiring the use of a specific decision aid under this NCD, we note that the National Institutes of Health's National Cancer Institute has developed a decision aid/tool, which is available at: http://www.cancer.gov/newscenter/qa/2002/NLSTstudyGuidePatientsPhysicians.

Reading Radiologist Training

Specific training and experience in performing LDCT screening and in interpreting results are important. The NLST had specific requirements for participating radiologists. Donnelly noted: "[l]ung cancer screening computed tomographies (CTs) differ from traditional chest CT scans in that they are performed at very low radiation doses, which allow the detection of small nodules but which have a much higher noise content that would not be acceptable in a diagnostic chest CT. The technical parameters require a great deal of attention on the part of the user, because inappropriate settings could result in either excess radiation dose to the large population of screened individuals or in low-quality images with impaired nodule detectability. Both situations undermine the main goal of the screening program, which is to detect lung nodules using as low a radiation dose as can reasonably be achieved. Once an image has been obtained, there are unique interpretive issues that must be addressed mainly because of the very high noise content of the images and the high prevalence of incidental findings in the chest unrelated to the sought-after pulmonary nodules."

To ensure that benefits outweigh the harms, specific furnishing and interpreting radiologist training is needed, consistent with the NLST. "Approval for NLST also required review of a dedicated NLST training set, created by a subgroup of radiologists, which described acceptable CT and chest radiographic acquisition parameters and image quality requirements, and provided examples of various focal lung opacities with corresponding interpretations to promote a uniform knowledge base across sites." (NLST, Radiology 2011) "Radiologist qualifications required certification by the American Board of Radiology or equivalent, documented training in diagnostic radiology and radiation safety, involvement in the supervision and interpretation of at least 300 chest CT acquisitions in the past 3 years and at least 200 chest radiographic acquisitions per year, and participation in continuing medical education in accordance with the American College of Radiology standard. Approval for NLST also required review of a dedicated NLST training set, created by a subgroup of radiologists, which described acceptable CT and chest radiographic acquisition parameters and image quality requirements, and provided examples of various focal lung opacities with corresponding interpretations to promote a uniform knowledge base across sites." (NLST, Radiology 2011. Supplemental Materials)

The American College of Radiology requires for CT accreditation board certification in radiology or diagnostic radiology or for radiologists that are not board certified "interpretation and reporting of 500 CT examinations in

the past 36 months' and other medical education (http://www.acr.org/~/media/ACR/Documents/Accreditation/CT/Requirements.pdf). To be an ACR Designated Lung Cancer Screening Center, the radiologist must have experience of interpreting "200 chest CT cases in prior 36 months:" (http://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/Lung%20Screening/Lung%20Cancer%20Screening%20Center%20Attestation%20Form.pdf).

Radiation Dose

An important aspect of LDCT screening is reducing radiation exposure to as low as reasonably achievable (ALARA; see http://www.nrc.gov/reading-rm/basic-ref/glossary/alara.html), especially given the annual screening frequency and likely follow-up diagnostic imaging tests. Donnelly noted: [i]n general, lower radiation doses can be achieved by using lower tube currents and lower tube voltages. The current-time product (mAs) can be considered as the number of x-rays that enter the patient. Use of fewer x-rays (lower mAs) results in a lower radiation dose to the patient but in a higher noise content to the image. Typical tube current-time product values for diagnostic studies vary greatly depending upon the institution, patient size, and other scanning parameters; however, these values are often in the 200 to 250 mAs range for an average-sized patient. In the NLST study, screening lung cancer CT scans were typically performed at 20 to 40 mAs."

"Although the acquisition parameters for low-dose CT are not explicitly defined in the imaging community, each of the scanners used in NLST was individually tested by using a CT dose index phantom and patient data to achieve comparable subjective image quality by using tube current–time products of 40 mAs or lower for the average-sized patient. Depending on the scanner, the effective tube current–time product (tube current–time products/scan pitch) range varied from 20 to 30 mAs for an average sized patient. It is estimated that each NLST low-dose CT resulted in an average effective dose of 1.5 mSv, whereas the effective dose from conventional chest CT varies considerably in clinical practice but is on the order of 8 mSv." (NLST, 2011 Radiology; Cody, 2010)

We received comments suggesting that the radiation dose should be as low as possible, and that CMS should allow for adjustments based on the size of the individual, along with suggesting that milligray (mGy) is a more common measurement than millisievert (mSv) for expressing volumetric dose. Based on the comments received and the evidence reviewed, including recently published multi-society, multi-disciplinary evidence-based recommendations (Kazerooni et al., 2014), we believe that LDCT with a volumetric CT dose index (CTDIvol) of ≤ 3.0 mGy (milligray) for standard size patients (defined to be 5' 7" tall; and approximately 155 pounds) with appropriate reductions in CTDIvol for smaller patients and appropriate increases in CTDIvol for larger patients, is appropriate for this Medicare benefit.

LDCT Lung Cancer Screening Imaging Facilities

Over the past few months, multi-society multi-disciplinary stakeholders, including major professional medical societies and NLST investigators, have worked collaboratively and intently to develop evidence-based recommendations on the necessary components of a high quality lung cancer screening program. Two recent published articles present guidance from these major stakeholders. Kazerooni et al. (2014) published the recommendations of the American College of Radiology with support in public comments from the Lung Cancer Alliance and the Society of Thoracic Surgeons. Mazzone et al. (2014) published recommendations from multispecialty stakeholders including the American College of Chest Physicians, American Thoracic Society, American Association of Thoracic Surgery, American Cancer Society and the American Society of Preventive Oncology. These evidence-based recommendations describe components that are necessary for high quality LDCT lung cancer screening programs. As reported, these components are:

Component 1: Who is offered LDCT lung cancer screening;
Component 2: How often, and for how long, to screen;
Component 3: How the CT is performed;
Component 4: Lung nodule identification;
Component 5: Structured reporting;
Component 6: Lung nodule management algorithms;
Component 7: Smoking cessation;
Component 8: Patient and provider education;
Component 9: Data collection.

Based on these recently published evidence-based recommendations, CMS strongly encourages eligible facilities to implement the necessary components of a high quality LDCT lung cancer screening program as recommended by multi-society stakeholders. In addition, we support the development of a multi-society, multi-disciplinary governance body to continue to refine and optimize screening practices over time. CMS would gladly participate.

We received feedback from commenters regarding the proposed imaging facility eligibility criteria. While we agree with some of the commenters that requiring past participation in the NLST or advanced diagnostic imaging center accreditation with experience in LDCT lung cancer screening would place an undue burden on imaging facilities, we also agree with the commenters who expressed concern that without quality requirements, beneficiaries could be exposed to additional harms. Based on the evidence reviewed, in response to the public comments, and to ensure appropriate access to these services, we have modified the imaging facility eligibility criteria. We believe these revised imaging facility eligibility requirements strike an appropriate balance between maintaining appropriate and high quality access to these services, while reducing burden.

For purposes of Medicare coverage of lung cancer screening with LDCT, an eligible imaging facility is one that:

- Performs LDCT with volumetric CT dose index (CTDIvol) of ≤ 3.0 mGy (milligray) for standard size patients (defined to be 5’ 7” and approximately 155 pounds) with appropriate reductions in CTDIvol for smaller patients and appropriate increases in CTDIvol for larger patients;
- Utilizes a standardized lung nodule identification, classification, and reporting system;
- Makes available smoking cessation interventions for current smokers; and

- Collects and submits data as described in this NCD to a CMS-approved national registry for each LDCT lung cancer screening performed.

LDCT Lung Cancer Screening Registry

The primary purpose for requiring the submission of data to the registry is to document compliance with the coverage criteria that are not evidenced on the health care claim. Furthermore, based on the public comments and the evidence reviewed, we strongly believe that the registry will serve as an aid to those seeking to study the clinical benefits of this screening. The registry and the other criteria required in this NCD are supported by the evidence reviewed, including the NLST. The registry will help ensure that only eligible beneficiaries will receive this screening service since only beneficiaries that meet the eligibility requirements will benefit from such screening.

Furthermore, we recognize the impact of this criterion for imaging facilities. We will only require production of the minimum number of data elements to carry out this payment function in an effort to reduce burdens. Therefore, we are modifying the data registry elements, based on our review of the evidence and feedback received from commenters. As amended, the data elements are limited to those required to determine whether an individual has met the coverage criteria for the LDCT lung cancer screening service, that is, whether their receipt of the service was "reasonable and necessary" and "appropriate." Data collected and submitted to a CMS-approved national registry must include, at minimum, all of the following elements:

Data Type	***Minimum Required Data Elements***
Facility	Identifier
Radiologist (reading)	National Provider Identifier (NPI)
Patient	Identifier
Ordering Practitioner	National Provider Identifier (NPI)
CT scanner	Manufacturer, Model

Data Type	*Minimum Required Data Elements*
Indication	Lung cancer LDCT screening – absence of signs or symptoms of lung cancer
System	Lung nodule identification, classification and reporting system
Smoking history	Current status (current, former, never), If former smoker, years since quitting, Pack-years as reported by the ordering practitioner, For current smokers, smoking cessation interventions available.
Effective radiation dose	CT Dose Index (CTDIvol)
Screening	Screen date Initial Screen or Subsequent Screen

Additionally, national registries are strongly encouraged to collect data on lung nodules (for example: clinically significant non-lung cancer findings, the number and types of nodules, and size and location of each nodule), subsequent diagnostic testing, adverse events, and intermediate and long term health outcomes, in order to inform practices and policymakers about the ability to implement a LDCT lung cancer screening program broadly in multiple settings across the country, and achieve positive outcomes, consistent with the NLST. We recognize that these other data elements are extremely important to establishing the benefit of these screening services and improvement in health outcomes. We strongly encourage submission of such data elements to registries in addition to the minimum elements required under this NCD. These data will not only verify that screening leads to improved health outcomes for the Medicare population, but will also serve as the basis to refine and improve screening in practice, and serve the quality improvement purposes of screening facilities. We believe that multi-society stakeholders are in the best position to determine the appropriate data elements for reaching these goals, and to adjust the particular elements over time.

All CMS-approved registries must have the capacity and capability to collect data from any Medicare-eligible imaging facility/department that furnishes lung cancer screening with LDCT, with a catchment area that includes all 50 States, United States Territories, and the District of Columbia. CMS will evaluate each entity interested in

participating as a CMS-approved registry to determine if they are capable of meeting the registry and data collection requirements outlined in this national coverage determination, including:

a. Establishment of a steering committee and a governance board for oversight of the registry;
b. Registry management plan, including identification of key personnel;
c. Operational plan and framework that describes mechanisms for collection and submission of data from imaging facilities to the registry;
d. Registry catchment area;
e. Mechanisms for the submission of registry data to CMS electronically;
f. Mechanisms to collect information (e.g.; HICN) in order to permit linkage of registry data with external databases (e.g. Medicare claims data sets);
g. Description of data management and data quality review methods, including validation;
h. Use of CMS-approved standardized data dictionary;
i. Mechanisms for submitting a list of facilities participating in the registry to CMS; and
j. Quality assurance plan.

Information regarding CMS-approved registries will be posted on the CMS website.

Adherence to Screening, Interval and Cumulative Screens

The NLST evaluated three annual LDCT screenings. DANTE and DLSCT evaluated five annual screenings. There is some consistency in the annual interval of screening studied in trials although there is little evidence to support an annual screen versus every two years or other interval. Results of ongoing trials in Europe may provide additional data in the future (Field, 2013). While the total number of annual screenings in these trials was likely influenced by trial logistics and funding, in addition to clinical considerations, the frequency and duration are important factors in adherence to a screening program over time. Adherence to screening protocols and programs is important to continually detect nodules over the study period. Adherence in the NLST was very high for all three screenings - "95 % in the low-dose CT group and 93 % in the radiography group" (NLST, 2011). If adherence is lower in general practice outside the clinical trial settings, the benefits of lung cancer screening, as demonstrated in the NLST, may be diminished.

Smoking Cessation

Since "[s]moking is widely recognized as the leading cause of lung cancer" (NCI - http://seer.cancer.gov/statfacts/html/lungb.html), smoking cessation interventions were integral interventions in published trials. According to the 2011 Medicare Current Beneficiary Survey (MCBS), 14 percent of beneficiaries reported to be current smokers, and 44 percent reported as former smokers, although pack-year information is not collected. Additionally, we received public comments that also addressed tobacco cessation interventions. Therefore, based on the evidence reviewed and public comments received, we are modifying the imaging facility eligibility criteria to require that smoking cessation interventions, such as educational materials, be made

available.

Additional Considerations

Expenditure Assessment

As noted in 42 CFR § 410.64, an assessment of the relation between predicted outcome and the expenditures of an additional preventive service may be conducted and the results of such assessment may be taken into consideration in making a national coverage determination regarding the coverage of a new preventive service. Cost and cost-effectiveness analyses have been conducted and published. McMahon et al. (2011) reported that "[a]nnual screening of current and former smokers aged 50–74 cost between $126,000–$169,000/QALY (minimum 20 pack-years of smoking) or $110,000–$166,000/QALY (40 pack-year minimum), compared to no screening and assuming background quit rates" and concluded that "[t]he cost-effectiveness of CT screening will likely be strongly linked to achievable smoking cessation rates. Trials and further modeling should explore the consequences of relationships between smoking behaviors and screen participation." Black et al. (2014) estimated that incremental cost-effectiveness ratios (ICERs) were $52,000 per life-year gained (95 % CI, 34,000 to 106,000). CMS will continue to closely monitor publications on expenditure assessments of lung cancer screening with LDCT.

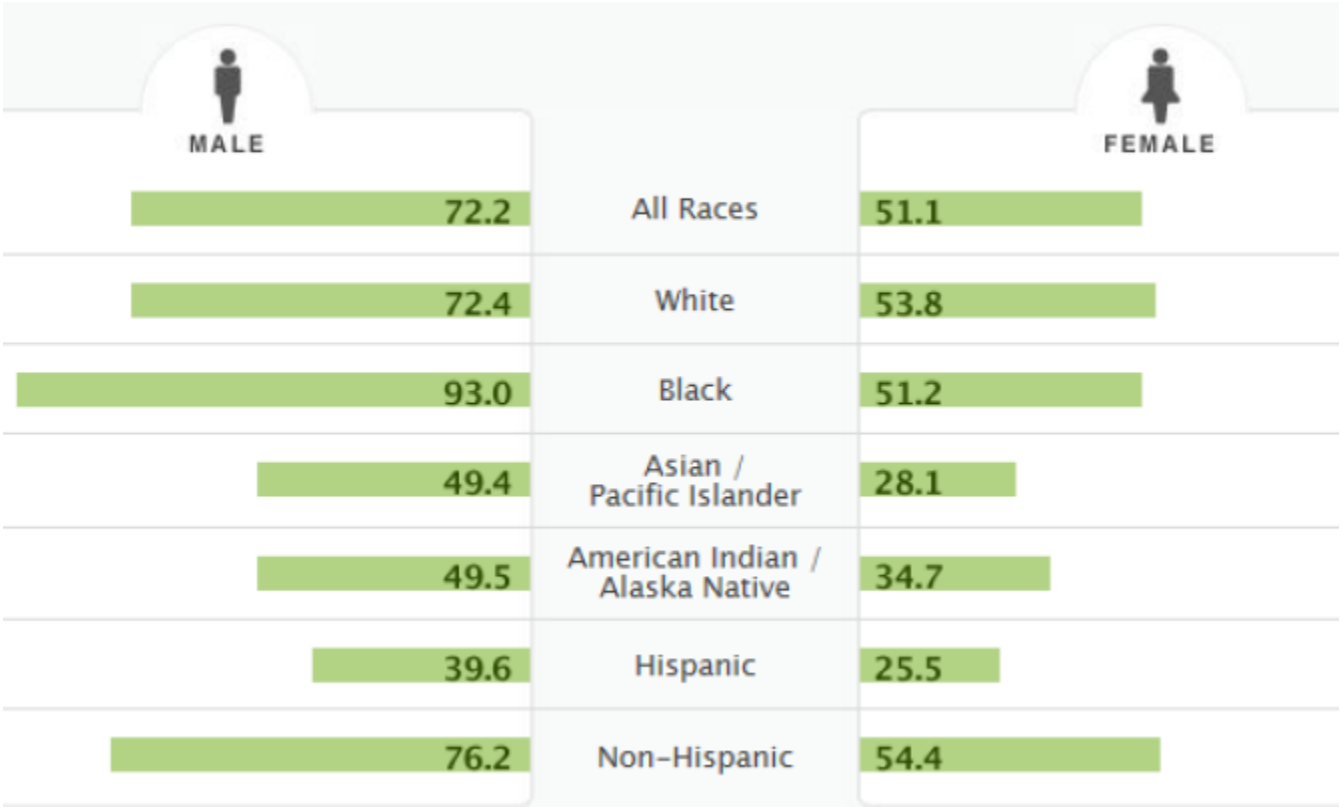
Post Coverage Analysis

In addition to the data to be collected to confirm screening eligibility, provider and center requirements, CMS will monitor benefits and harms using administrative and clinical databases such as SEER and/or U.S. Cancer Statistics as necessary to ensure that benefits continue to outweigh harms when lung cancer LDCT screening is implemented broadly outside the controlled trial setting, and when screening data accumulates beyond the three annual screens seen in the NLST. Without continuing outcomes evaluation, there is insufficient evidence to support screening greater than three annual LDCT lung cancer screenings. CMS will evaluate five year data to better establish duration and the cumulative limit in the number of LDCT screens, as well as inform, if appropriate, modifications to Medicare coverage.

Disparities

Lung cancer incidences are more common in men than women, and highest in African American men. Women comprised 41 percent of the study population in NLST. We note that 90.9 percent of participants in the NLST were white. CMS encourages shared decision making between patients and practitioners, and if appropriate, participation in a lung cancer screening program.

Number of New Cases per 100,000 Persons by Race/Ethnicity & Sex: Lung and Bronchus Cancer (SEER 18, 2007-2011, Age-Adjusted)



http://seer.cancer.gov/statfacts/html/lungb.html

Summary

Given the burden of lung cancer on the United States population, a suitable screening test for lung cancer has been sought for many years. Lung cancer screening has been recommended by the USPSTF with a grade B recommendation for certain individuals. Based on our review of the available evidence, including clinical guidelines and public comments, we find that the evidence is sufficient to conclude that lung cancer screening with LDCT is reasonable and necessary for prevention or early detection of illness or disability and appropriate for Medicare beneficiaries under conditions established in this NCD. These conditions are supported by the evidence reviewed, including conditions in the NLST and evidence-based multi-society, multi-disciplinary recommendations. The results of ongoing trials will provide additional evidence. We believe that specific

beneficiary, practitioner, and imaging facility eligibility requirements are necessary to ensure that benefits of screening outweigh harms in the Medicare population, consistent with the NLST. Lung cancer screening with LDCT has not been implemented broadly in any population to date. While we are establishing coverage for this additional preventive service under Medicare part B, we believe we need to proceed in a responsible manner and will continue to monitor the evidence as stewards of the Medicare program.

IX. Conclusion

The Centers for Medicare & Medicaid Services (CMS) has determined that the evidence is sufficient to add a lung cancer screening counseling and shared decision making visit, and for appropriate beneficiaries, annual screening for lung cancer with low dose computed tomography (LDCT), as an additional preventive service benefit under the Medicare program only if all of the following criteria are met:

Beneficiary eligibility criteria:

- Age 55 – 77 years;
- Asymptomatic (no signs or symptoms of lung cancer);
- Tobacco smoking history of at least 30 pack-years (one pack-year = smoking one pack per day for one year; 1 pack = 20 cigarettes);
- Current smoker or one who has quit smoking within the last 15 years; and
- Receives a written order for LDCT lung cancer screening that meets the following criteria:

- *For the initial LDCT lung cancer screening service:* a beneficiary must receive a written order for LDCT lung cancer screening during a lung cancer screening counseling and shared decision making visit, furnished by a physician (as defined in Section 1861(r)(1) of the Social Security Act) or qualified non-physician practitioner (meaning a physician assistant, nurse practitioner, or clinical nurse specialist as defined in §1861(aa)(5) of the Social Security Act). A lung cancer screening counseling and shared decision making visit includes the following elements (and is appropriately documented in the beneficiary's medical records):
    - Determination of beneficiary eligibility including age, absence of signs or symptoms of lung cancer, a specific calculation of cigarette smoking pack-years; and if a former smoker, the number of years since quitting;
    - Shared decision making, including the use of one or more decision aids, to include benefits and harms of screening, follow-up diagnostic testing, over-diagnosis, false positive rate, and total radiation exposure;
    - Counseling on the importance of adherence to annual lung cancer LDCT screening, impact of comorbidities and ability or willingness to undergo diagnosis and treatment;
    - Counseling on the importance of maintaining cigarette smoking abstinence if former smoker; or the importance of smoking cessation if current smoker and, if appropriate, furnishing of information about tobacco cessation interventions; and
    - If appropriate, the furnishing of a written order for lung cancer screening with LDCT.
- *For subsequent LDCT lung cancer screenings:* the beneficiary must receive a written order for LDCT lung cancer screening, which may be furnished during any appropriate visit with a physician (as defined in Section 1861(r)(1) of the Social Security Act) or qualified non-physician practitioner (meaning a physician assistant, nurse practitioner, or clinical nurse specialist as defined in Section 1861(aa)(5) of the Social Security Act). If a physician or qualified non-physician practitioner elects to provide a lung cancer screening counseling and shared decision making visit for subsequent lung cancer screenings with LDCT, the visit must meet the criteria described above for a counseling and shared decision making visit.
- Written orders for both initial and subsequent LDCT lung cancer screenings must contain the following information, which must also be appropriately documented in the beneficiary's medical records:
    - Beneficiary date of birth;
    - Actual pack - year smoking history (number);
    - Current smoking status, and for former smokers, the number of years since quitting smoking;
    - Statement that the beneficiary is asymptomatic (no signs or symptoms of lung cancer); and
    - National Provider Identifier (NPI) of the ordering practitioner.

Reading radiologist eligibility criteria:

- Board certification or board eligibility with the American Board of Radiology or equivalent organization;
- Documented training in diagnostic radiology and radiation safety;
- Involvement in the supervision and interpretation of at least 300 chest computed tomography acquisitions in the past 3 years;
- Documented participation in continuing medical education in accordance with current American College of Radiology standards; and
- Furnish lung cancer screening with LDCT in a radiology imaging facility that meets the radiology imaging facility eligibility criteria below.

Radiology imaging facility eligibility criteria:

- Performs LDCT with volumetric CT dose index (CTDIvol) of ≤ 3.0 mGy (milligray) for standard size patients (defined to be 5' 7" and approximately 155 pounds) with appropriate reductions in CTDIvol for smaller patients and appropriate increases in CTDIvol for larger patients;
- Utilizes a standardized lung nodule identification, classification and reporting system;

- Makes available smoking cessation interventions for current smokers; and
- Collects and submits data to a CMS-approved registry for each LDCT lung cancer screening performed. The data collected and submitted to a CMS-approved registry must include, at minimum, all of the following elements:

Data Type	***Minimum Required Data Elements***
Facility	Identifier
Radiologist (reading)	National Provider Identifier (NPI)
Patient	Identifier
Ordering Practitioner	National Provider Identifier (NPI)
CT scanner	Manufacturer, Model.
Indication	Lung cancer LDCT screening – absence of signs or symptoms of lung cancer
System	Lung nodule identification, classification and reporting system
Smoking history	Current status (current, former, never). If former smoker, years since quitting. Pack-years as reported by the ordering practitioner. For current smokers, smoking cessation interventions available.
Effective radiation dose	CT Dose Index (CTDIvol).

Data Type	*Minimum Required Data Elements*
Screening	Screen date Initial screen or subsequent screen

All CMS-approved registries must have the capacity and capability to collect data from any Medicare-eligible imaging facility/department that furnishes lung cancer screening with LDCT, with a catchment area that includes all 50 States, United States Territories, and the District of Columbia. CMS will evaluate each entity interested in participating as a CMS-approved registry to determine if they are capable of meeting the registry and data collection requirements outlined in this national coverage determination, including:

a. Establishment of a steering committee and a governance board for oversight of the registry;
b. Registry management plan, including identification of key personnel;
c. Operational plan and framework that describes mechanisms for collection and submission of data from imaging facilities to the registry;
d. Registry catchment area;
e. Mechanisms for the submission of registry data to CMS electronically;
f. Mechanisms to collect information (e.g.; HICN) in order to permit linkage of registry data with external databases (e.g. Medicare claims data sets);
g. Description of data management and data quality review methods, including validation;
h. Use of CMS-approved standardized data dictionary;
i. Mechanisms for submitting a list of facilities participating in the registry to CMS; and
j. Quality assurance plan.

To apply to function as a CMS-approved registry, interested entities must submit a letter of interest along with detailed supporting information about how the interested entity is able to meet the requirements outlined in this national coverage determination to the following address or via email to caginquiries@cms.hhs.gov.

Centers for Medicare & Medicaid Services
Center for Clinical Standards and Quality
Director, Coverage and Analysis Group
ATTN: Lung Cancer LDCT Screening
Mail Stop: S3-02-01
7500 Security Blvd.
Baltimore, MD 21244

Information regarding CMS-approved registries will be posted on the CMS website.

Appendix A

Articles/References Submitted by the Requestors

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Appendix C

This information is representative of Medicare's national coverage determination (NCD) for implementation purposes only. The information is subject to formal revisions and formatting changes prior to the release of the final NCD contractor instructions and publication in the Medicare National Coverage Determinations Manual.

Screening for Lung Cancer with Low Dose Computed Tomography (LDCT)

Item/Service Description

A. General

Lung cancer is the third most common cancer and the leading cause of cancer deaths in the United States. Cancer of the lung and bronchus accounted for over 150,000 deaths in 2013, with a median age at death of 72 years. Computed tomography (CT) is an imaging procedure that uses specialized x-ray equipment to create detailed pictures of areas inside the body. Low dose computed tomography (LDCT) is a chest CT scan performed at settings to minimize radiation exposure compared to a standard chest CT.

Under §1861(ddd) of the Social Security Act (the Act), the Centers for Medicare & Medicaid Services (CMS) has the authority to add coverage of additional preventive services if certain statutory requirements are met. The regulations provide:

42 CFR § 410.64 Additional preventive services

(a) Medicare Part B pays for additional preventive services not described in paragraph (1) or (3) of the definition of "preventive services" under §410.2, that identify medical conditions or risk factors for individuals if the Secretary determines through the national coverage determination process (as defined in section 1869(f)(1)(B) of the Act) that these services are all of the following: (1) reasonable and necessary for the prevention or early detection of illness or disability.(2) recommended with a grade of A or B by the United States Preventive Services Task Force, (3) appropriate for individuals entitled to benefits under Part A or enrolled under Part B.

(b) In making determinations under paragraph (a) of this section regarding the coverage of a new preventive

service, the Secretary may conduct an assessment of the relation between predicted outcomes and the expenditures for such services and may take into account the results of such an assessment in making such national coverage determinations.

The scope of the national coverage analysis evaluated the evidence for screening for lung cancer with LDCT. Diagnostic CTs were outside the scope of the national coverage analysis.

Indications and Limitations of Coverage

B. Nationally Covered Indications

The Centers for Medicare & Medicaid Services (CMS) has determined that the evidence is sufficient to add a lung cancer screening counseling and shared decision making visit, and for appropriate beneficiaries, annual screening for lung cancer with low dose computed tomography (LDCT), as an additional preventive service benefit under the Medicare program only if all of the following criteria are met:

Beneficiary eligibility criteria:

•Age 55 – 77 years;
•Asymptomatic (no signs or symptoms of lung cancer);
•Tobacco smoking history of at least 30 pack-years (one pack-year = smoking one pack per day for one year; 1 pack = 20 cigarettes);
•Current smoker or one who has quit smoking within the last 15 years; and
•Receives a written order for LDCT lung cancer screening that meets the following criteria:

- *For the initial LDCT lung cancer screening service:* a beneficiary must receive a written order for LDCT lung cancer screening during a lung cancer screening counseling and shared decision making visit, furnished by a physician (as defined in Section 1861(r)(1) of the Social Security Act) or qualified non-physician practitioner (meaning a physician assistant, nurse practitioner, or clinical nurse specialist as defined in §1861(aa)(5) of the Social Security Act). A lung cancer screening counseling and shared decision making visit includes the following elements (and is appropriately documented in the beneficiary's medical records):

    - Determination of beneficiary eligibility including age, absence of signs or symptoms of lung cancer, a specific calculation of cigarette smoking pack-years; and if a former smoker, the number of years since quitting;
    - Shared decision making, including the use of one or more decision aids, to include benefits and harms of screening, follow-up diagnostic testing, over-diagnosis, false positive rate, and total radiation exposure;
    - Counseling on the importance of adherence to annual lung cancer LDCT screening, impact of comorbidities and ability or willingness to undergo diagnosis and treatment;
    - Counseling on the importance of maintaining cigarette smoking abstinence if former smoker; or the importance of smoking cessation if current smoker and, if appropriate, furnishing of information about tobacco cessation interventions; and
    - If appropriate, the furnishing of a written order for lung cancer screening with LDCT.
- *For subsequent LDCT lung cancer screenings:* the beneficiary must receive a written order for LDCT lung cancer screening, which may be furnished during any appropriate visit with a physician (as defined in Section 1861(r)(1) of the Social Security Act) or qualified non-physician practitioner (meaning a physician assistant, nurse practitioner, or clinical nurse specialist as defined in Section 1861(aa)(5) of the Social Security Act). If a physician or qualified non-physician practitioner elects to provide a lung cancer screening counseling and shared decision making visit for subsequent lung cancer screenings with LDCT, the visit must meet the criteria described above for a counseling and shared decision making visit.
- Written orders for both initial and subsequent LDCT lung cancer screenings must contain the following information, which must also be appropriately documented in the beneficiary's medical records:
    - Beneficiary date of birth;
    - Actual pack - year smoking history (number);
    - Current smoking status, and for former smokers, the number of years since quitting smoking;
    - Statement that the beneficiary is asymptomatic (no signs or symptoms of lung cancer); and
    - National Provider Identifier (NPI) of the ordering practitioner.

Reading radiologist eligibility criteria:

- Board certification or board eligibility with the American Board of Radiology or equivalent organization;
- Documented training in diagnostic radiology and radiation safety;
- Involvement in the supervision and interpretation of at least 300 chest computed tomography acquisitions in the past 3 years;
- Documented participation in continuing medical education in accordance with current American College of Radiology standards; and
- Furnish lung cancer screening with LDCT in a radiology imaging facility that meets the radiology imaging facility eligibility criteria below.

Radiology imaging facility eligibility criteria:

- Performs LDCT with volumetric CT dose index (CTDIvol) of ≤ 3.0 mGy (milligray) for standard size patients (defined to be 5' 7" and approximately 155 pounds) with appropriate reductions in CTDIvol for smaller patients and appropriate
- increases in CTDIvol for larger patients;
- Utilizes a standardized lung nodule identification, classification and reporting system;
- Makes available smoking cessation interventions for current smokers; and
- Collects and submits data to a CMS-approved registry for each LDCT lung cancer screening performed. The data collected and submitted to a CMS-approved registry must include, at minimum, all of the following elements:

Data Type	***Minimum Required Data Elements***
Facility	Identifier

Data Type	*Minimum Required Data Elements*
Radiologist (reading)	National Provider Identifier (NPI)
Patient	Identifier
Ordering Practitioner	National Provider Identifier (NPI)
CT scanner	Manufacturer, Model.
Indication	Lung cancer LDCT screening – absence of signs or symptoms of lung cancer
System	Lung nodule identification, classification and reporting system
Smoking history	Current status (current, former, never). If former smoker, years since quitting. Pack-years as reported by the ordering practitioner. For current smokers, smoking cessation interventions available.
Effective radiation dose	CT Dose Index (CTDIvol).
Screening	Screen date Initial screen or subsequent screen

All CMS-approved registries must have the capacity and capability to collect data from any Medicare-eligible imaging facility/department that furnishes lung cancer screening with LDCT, with a catchment area that includes all 50 States, United States Territories, and the District of Columbia. CMS will evaluate each entity interested in participating as a CMS-approved registry to determine if they are capable of meeting the registry and data collection requirements outlined in this national coverage determination, including:

a. Establishment of a steering committee and a governance board for oversight of the registry;
b. Registry management plan, including identification of key personnel;
c. Operational plan and framework that describes mechanisms for collection and submission of data from imaging facilities to the registry;
d. Registry catchment area;
e. Mechanisms for the submission of registry data to CMS electronically;
f. Mechanisms to collect information (e.g.; HICN) in order to permit linkage of registry data with external databases (e.g. Medicare claims data sets);
g. Description of data management and data quality review methods, including validation;
h. Use of CMS-approved standardized data dictionary;
i. Mechanisms for submitting a list of facilities participating in the registry to CMS; and
j. Quality assurance plan.

To apply to function as a CMS-approved registry, interested entities must submit a letter of interest along with detailed supporting information about how the interested entity is able to meet the requirements outlined in this national coverage determination to the following address or via email to caginquiries@cms.hhs.gov.

Centers for Medicare & Medicaid Services
Center for Clinical Standards and Quality
Director, Coverage and Analysis Group
ATTN: Lung Cancer LDCT Screening
Mail Stop: S3-02-01
7500 Security Blvd.
Baltimore, MD 21244

Information regarding CMS-approved registries will be posted on the CMS website.

C. Nationally Non-Covered Indications

Unless specifically covered in this NCD, any other NCD, or in statute, preventive services are non-covered by Medicare.

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Section 5.0

New Discussion Items

Question: should the coding specification on line 449 ADJUSTMENT DISORDERS be deleted? Should various codes used for early childhood intervention be added to line 449?

Question source: BHAP, HERC staff, OHA foster care division, provider

Issue: at the September, 2015 BHAP meeting, it was brought up that the coding specification on line 449 ADJUSTMENT DISORDERS contained ICD-10 codes that were not included on this line. HSD staff requested that Z63.4 (Disappearance and death of family member) be added to line 449 at allow counseling for children in foster care who are removed from their family. On review, HERC staff found that the coding specification, written in ICD-9, is not workable in ICD-10. The ICD-9 V codes referenced in the original coding specification were required to be secondary codes; the ICD-10 Z codes which were cross-walked from these ICD-9 codes can be used as primary codes. Therefore, requiring these ICD-10 codes to be listed as secondary results in a requirement for improper coding. One of the cross-walked Z codes, Z71.89 (Other specified counseling) is on line 449 and needs to be removed as it will result in pairing of this code with counseling CPT codes which is inappropriate.

As an Errata, the two referenced ICD-10 codes in the coding specification that were missing from line 449 were added to line 449.

Line 449 coding specification

> CD-10-CM codes Z71.89, Other specified counseling, and Z63.4 Disappearance and death of family member are only included in this line when identified as secondary diagnoses with a primary diagnosis of F43.8, Other reactions to severe stress.

Diagnoses included on line 449 ADJUSTMENT DISORDERS

ICD-10 Code	**Code description**
F43.2x	Adjustment disorder
F43.8	Other reactions to severe stress
Z63.4	Disappearance and death of family member
Z71.89	Other specified counseling

Further information from HSD staff:

> We spoke briefly after the HERC Behavioral Health Subcommittee meeting about the work that OHA is doing to expand services to children birth through five years old. You asked me to send you some information about codes that the group really needs available for reimbursement in order to meet the goals for mental health services for children 0-5.
>
> Of course, common mental health disorders can be diagnosed in very young children such as depression and separation anxiety. However, some less specific diagnostic codes are needed for young children for circumstances that because of their age, we would have to wait until they moved into a new developmental stage and their symptoms worsened before they could get the help they need. Aside from the Child Maltreatment and Neglect codes that I know are being moved into the PTSD line (previously 995. Codes), below are the Z codes and "Other Specified" codes that are often appropriate for 0-5 when they may not be specific enough for older clients.

F43.8 Other Specified Trauma and Stressor Related Disorder-Bereavement- The intent was to provide therapeutic supports to a child or family when there was a loss or change in primary caregiver.
F91-8- Other Specified Disruptive, Impulse Control and Conduct Disorder (Previously Disruptive behavior D/O NOS)
Z62.820- Parent Child Relational Problem
Z63.8- Other Specified Problems related to the primary support group

From Kevin Burns, Child & Family Therapist

My primary concern is the loss of two diagnosis the allow us to serve young children with primarily significant behavioral problems, and the absence of any identified "adjustment" reaction. Many of these children do not meet criteria for ADHD, or PTSD, and even when they do, these diagnosis can sometimes be "heavier" than necessary for a 2-3 year old.

We frequently see children from dysfunctional family systems, with no direct trauma history associated with the child, who are so unregulated with their emotional energy, they are disrupting their family and preschool functioning. The diagnosis of Unspecified Behavioral and Emotional Disorder (F91.9) and Disruptive Behavior Disorder NOS (F98.9), previously listed above the priority list line, are now below the line. These codes can be very useful in providing services to young children using a developmentally appropriate lens to organize their treatment.

I encourage the Value-Based Subcommittee to support the States (previously OHA) 2015-2018 Behavioral Health Strategic Plan that promotes Early Intervention and prevention efforts listed under section 3. I believe having enough 0-5 focused diagnosis available to work with children and families is important so we can limit the # of kids who "fall through the cracks" when trying to access appropriate services.

<u>List information</u>:

F91.8 (Other conduct disorders) is on line 483 CONDUCT DISORDER, AGE 18 OR UNDER
Note: the ICD-9 equivalent 312.89 (Other conduct disorder) has been on line 483 for some time
F91.9 (Conduct disorder, unspecified) is on line 483 CONDUCT DISORDER, AGE 18 OR UNDER
Note: the ICD-9 equivalent 312.9 (Unspecified disturbance of conduct) is on line 425 OPPOSITIONAL DEFIANT DISORDER
Note: per coding specifications, this code should be used for conduct and behavioral disorders NOS as well as abnormal behavior NOS
F98.9 (Unspecified behavioral and emotional disorders with onset usually occurring in childhood and adolescence) is on the HSD Undefined File
Z62.8x (Parent-child conflict) is in the HSD Informational File
Z63.8 (Other specified problems related to primary support group) is in the HSD Informational File

HERC staff recommendations:

1) Delete the coding specification from line 449 ADJUSTMENT DISORDERS
    a. Z codes can be used as primary billing codes
2) Delete Z71.89 (Other specified counseling) from line 449 ADJUSTMENT DISORDERS
    a. Advise HSD to add Z71.89 to the Informational File
    b. This code allows "circular" coding with the CPT code for counseling on this line
3) Keep F43.2x (Adjustment disorder), F43.8 (Other reactions to severe stress), and Z63.4 (Disappearance and death of family member) on line 449 ADJUSTMENT DISORDERS
4) Add Z62.8x (Parent-child conflict) and Z63.8 (Other specified problems related to primary support group) and F98.9 (Unspecified behavioral and emotional disorders with onset usually occurring in childhood and adolescence) to line 449 ADJUSTMENT DISORDERS
    a. Advise HSD to remove Z62.8x and Z63.8 from the Informational File
    b. Advise HSD to remove F98.9 form the Unspecified File
5) Add F91.9 (Conduct disorder, unspecified) to line 425 OPPOSITIONAL DEFIANT DISORDER and delete from line 483 CONDUCT DISORDER, AGE 18 OR UNDER
    a. Alternately: add F91.9 to line 425 and keep on line 483 with a guideline note as shown below

GUIDELINE NOTE XXX UNSPECIFIED CONDUCT DISORDER

Lines 425, 483

ICD-10 F91.9 (Conduct disorder, unspecified) is included on line 425 only for children ages 5 and younger who cannot be diagnosed with a more specific mental health diagnosis. This diagnosis is included on line 483 for older children, adolescents, and adults.

Thromboangiitis obliterans [Buerger's disease]

Issue: Buerger's disease or thromboangiitis obliterans (ICD-10 I73.1) was on lines 117: GIANT CELL ARTERITIS, AND KAWASAKI DISEASE; THROMBOANGIITIS OBLITERANS 172: PREVENTIVE FOOT CARE IN HIGH RISK PATIENTS, and 270: ARTERIAL EMBOLISM/THROMBOSIS: ABDOMINAL AORTA, THORACIC AORTA. The ICD-10 Rheumatology review removed these codes from all of these lines and placed it on line 685: CARDIOVASCULAR CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY and renamed line 117 GIANT CELL ARTERITIS, POLYMYALGIA RHEUMATICA, AND KAWASAKI DISEASE ~~THROMBOANGIITIS OBLITERANS.~~ The ICD-9 equivalent, 443.1 Thromboangiitis obliterans (Buerger's disease), was never moved. The rationale for moving Buerger's disease to an uncovered line was that there is no treatment for Buerger's disease other than smoking cessation. However, several CCO's have complained about the loss of coverage with the October 1, 2015 Prioritized List. They are getting requests for wound care and other therapy for Buerger's disease.

Recent reviews on the topic outline various therapies, including amputation, medications, immunotherapy, and hyperbaric oxygen therapy. Dargon (2012) critically reviewed the literature and concluded that "Tobacco cessation is the cornerstone of treatment. Other modalities of reducing pain or avoiding amputation have not been as successful."

Complications of Buerger's disease such as ulcerations or gangrene could be coded with other diagnosis codes, such as peripheral vascular disease with gangrene. However, this may not be correct coding convention.

Treatments on line 240 include amputations, revascularization procedures, bypass grafts, embolectomy, and angioplasty. The evidence for treatment of Buerger's disease finds that revascularization and bypass graft procedures are not successful, mainly due to the lack of good targets as a result of disease. Including Buerger's disease on a covered line would allow coverage of wound care and other supportive care activities as well as office visits and hospitalization.

HERC staff recommendations:

1) Add ICD-10 I73.1 (Buerger's disease) to line 240 LIMB THREATENING VASCULAR DISEASE, INFECTIONS, AND VASCULAR COMPLICATIONS and keep on line 657 CARDIOVASCULAR CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
2) Adopt the following new guideline note

GUIDELINE NOTE XXX BUERGER'S DISEASE

Lines 240, 657

Buerger's disease (ICD-10 I73.1) is included on line 240 only when ulceration or gangrene is present. Otherwise, this diagnosis is included on line 657. TI73.1 does not pair on line 240 with revascularization procedures, bypass graft procedures, or angioplasty.

ELSEVIER

Basic Data Underlying Clinical Decision-Making in Endovascular Therapy

Buerger's Disease

Phong T. Dargon,[1] and Gregory J. Landry,[2] Portland, Oregon

Buerger's disease (thromboangiitis obliterans) is a nonatherosclerotic segmental inflammatory disease of small- and medium-sized arteries of the distal extremities of predominantly young male tobacco users. Early symptoms may include episodic pain and coldness in fingers, and late findings may present as intermittent claudication, skin ulcers, or gangrene requiring eventual amputation. Tobacco cessation is the cornerstone of treatment. Other modalities of reducing pain or avoiding amputation have not been as successful. This review summarizes in tabular form the types of treatment that have been used, including therapeutic angiogenesis.

INTRODUCTION

Buerger's disease (thromboangiitis obliterans) is a nonatherosclerotic segmental inflammatory disease of small- and medium-sized arteries of the distal extremities of male tobacco users.[1] It was first described by Felix Von Winiwarter in 1879. In 1908, Leo Buerger published a detailed pathologic description of 11 amputated limbs.[2] Buerger's disease typically affects young male smokers; however, there is an increasing prevalence in women. It is more prevalent in the Middle East and Far East than in North America and Western Europe.

Patients may present with early findings of pain or coldness in the fingers. Later findings include rest pain, skin ulcers, gangrene, and eventual amputation. The Shionoya clinical diagnostic criteria are as follows: (1) smoking history, (2) onset before the age of 50 years, (3) infrapopliteal arterial occlusions, (4) either upper limb involvement or phlebitis migrans, and (5) absence of atherosclerotic risk factors other than smoking.[3] A wider subset of major and minor criteria for the diagnosis of Buerger's disease, described by Mills and Porter, is listed in

Table I. Criteria for diagnosis of Buerger's disease[4]

Major criteria
Onset of distal extremity ischemic symptoms before age 45 years
Tobacco use
Exclusion of:
Proximal embolic source (cardiac, TOS, ASO, aneurysms)
Trauma and local lesions (entrapment, adventitial cyst)
Autoimmune disease
Hypercoagulable states
Atherosclerosis
Atherosclerotic risk factors (diabetes, hypertension, hyperlipidemia)
No evidence of arterial disease proximal to popliteal or distal brachial arteries
Objective documentation of distal occlusive disease by either:
Plethysmography
Histopathology
Arteriography
Minor criteria
Migratory superficial phlebitis
Raynaud's syndrome
Upper extremity involvement
Instep claudication

TOS, thoracic outlet syndrome; ASO, arteriosclerosis obliterans.

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Section 6.0

Guidelines

Acupuncture Guideline Modifications

Questions:

1) Should the requirement for referral be removed from the Acupuncture guidelines for non-maternity indications?
2) Should the limit of 2 visits for hyperemesis and breech presentation be increased?
3) How should the acupuncture guideline be modified to align with the back line changes?

Question source: HERC staff

Issue:

The acupuncture guideline was discussed at the October, 2015 VBBS meeting. At that time, the staff suggestion was to remove the clause "with referral" in most of the sections. This was received with some concern by the VBBS, and HERC staff was directed to determine if acupuncturists could use E&M codes and generate diagnoses. There was also concern with removing "with referral" for pelvic pain in pregnancy; the general consensus was that maternity care conditions should continue to require referral.

There was also a proposal to remove the current limit of 2 visits for hyperemesis and breech presentation. These restrictions were added initially due to concern for overutilization and the possibility of the acupuncturist being able to teach the patient techniques to use at home. All other indications allow 12 visits, with the exception of depression for which 15 visits are allowed. At the October, 2015 meeting, the VBBS was generally favorable to this change.

It was brought to HERC staff attention at the October meeting that the back pain entries in the acupuncture guideline do not reflect the changes made to the coverage of acupuncture for pain conditions with the reworking of the back lines. The new back lines guideline allows up to 30 visits for a combination of PT, chiropractic, and acupuncture services. The acupuncture guideline should be revised to reflect these changes. Additionally, the back line changes are on hold for an indefinite period and therefore HERC staff feel that 2 versions of these guidelines should be created, one to be in effect prior to the implementation of the back lines changes and one version to be in effect once the back lines changes are in effect.

Since the October, 2015 meeting, HERC staff has received written testimony from Stuart Greenleaf, Lac, which provides support to the removal of the "by referral" clause, and additionally requests multiple changes and updates to the guideline. Among the changes he recommends are

1) Changing the ICD-10 code listed for migraine. The current code (G43.9) codes only for unspecified migraine.
2) Suggested spelling out all code descriptions to assist PCPs
3) Clarify that some of the entries are for below the funding line diagnoses and therefore not covered
4) Correcting multiple incorrect ICD-10 codes in the back line entries
5) Adding ICD-10 codes for the knee osteoarthritis line

6) Correct the lumbar spine ICD-10 codes for line 545 as all are incorrect and not currently on the line

HERC staff recommendations:

1) Modify GN92 as shown below [note: 2 versions are shown, due to delay in new back line implementation]
    a. Remove requirement for referral from all but obstetric indications
    b. Make all coverage uniform at 12 visits, except back conditions
    c. Correct the diagnosis codes for line 374
    d. Include all migraine diagnosis codes for line 415
    e. Adding in the ICD-10 code for osteoarthritis of the knee for line 467
    f. Correct the lumbar back ICD-10 diagnosis codes for line 545
    g. Affirm the changes made to the back pain lines as previously accepted with the back lines reorganization to take effect when the new back line implementation occurs (changes in purple were already approved)

For January 1, 2016 Prioritized List, but referencing October 1, 2015 back line changes due to implementation delay.

GUIDELINE NOTE 92, ACUPUNCTURE

Lines 1, 20~~7~~8,374, 41~~4~~5, 46~~8~~7,545, 54~~6~~3

Inclusion of acupuncture (CPT 97810-97814) on the Prioritized List has the following limitations:

Line 1 PREGNANCY

Acupuncture pairs on Line 1 for the following conditions and codes.

Hyperemesis gravidarum

ICD-10-CM code: O21.0, O21.1

Acupuncture pairs with hyperemesis gravidarum when a diagnosis is made by the maternity care provider and referred for acupuncture treatment for up to ~~2~~ 12 sessions of acupressure/acupuncture.

Breech presentation

ICD-10-CM code: O32.1xx0, O32.8xx0

Acupuncture (and moxibustion) is paired with breech presentation when a referral with a diagnosis of breech presentation is made by the maternity care provider, the patient is between 33 and 38 weeks gestation, for up to ~~2~~ 12 visits.

Back and pelvic pain of pregnancy

ICD-10-CM code: O33.0

Acupuncture is paired with back and pelvic pain of pregnancy when referred by maternity care provider/primary care provider for up to 12 sessions.

Line 20~~7~~8 DEPRESSION AND OTHER MOOD DISORDERS, MILD OR MODERATE

Acupuncture is paired with the treatment of post-stroke depression only. Treatments may be billed to a maximum of 30 minutes face-to-face time and limited to ~~15~~ 12 total sessions, with documentation of meaningful improvement.

Acupuncture Guideline Modifications

From October 1, 2015 Prioritized List Line 374 DISORDERS OF SPINE WITH NEUROLOGIC IMPAIRMENT

Acupuncture is included on Line 374 only for pairing with disorders of the spine with myelopathy and/or radiculopathy represented by the diagnosis codes G83.4, ~~M47.1x,~~ M47.2x, M50.0x, M50.1x, M51.0x, M51.1x, M54.1x) ~~with referral,~~ for up to 12 sessions.

Line 41~~4~~5 MIGRAINE HEADACHES

Acupuncture pairs on Line 41~~4~~5 for ~~G43.9~~ Migraine (ICD-10-CM code G43.0xx, G43.1xx, G43.5xx, G43.7xx, G43.8xx, G43.9xx), ~~when referred,~~ for up to 12 sessions.

Line 46~~8~~7 OSTEOARTHRITIS AND ALLIED DISORDERS

Acupuncture pairs on Line 46~~8~~7 for osteoarthritis of the knee only (ICD-10 code M17.xx) ~~, when referred,~~ for up to 12 sessions.

* *From October 1, 2015 Prioritized List* Line 545 ACUTE AND CHRONIC DISORDERS OF SPINE WITHOUT NEUROLOGIC IMPAIRMENT

Acupuncture pairs on Line 545 with the low back diagnoses (ICD-10-CM codes ~~G83.4, M47.1x, M47.2x, M50.0x, M50.1x, M51.1x, M54.1x~~, M51.36, M51.86, M54.5, M99.03,S33.5xxx, S33.9xxx, S39.092x,S39.82xx, S39.92xx), ~~when referred,~~ for up to 12 sessions. Acupuncture pairs with chronic (>90 days) neck pain diagnoses (ICD-10-CM M53.82, M54.2, S13.4XXX, S13.8XXX) ~~, when referred~~, for up to 12 sessions.

*Line 54~~6~~3 TENSION HEADACHES

Acupuncture is included on Line 54~~6~~3 for treatment of tension headaches (ICD-10-CM G44.2x) ~~, when referred,~~ for up to 12 sessions.

The development of this guideline note was informed by a HERC evidence-based guideline. See http://www.oregon.gov/oha/herc/Pages/blog-low-back-non-pharmacologic-intervention.aspx

*Below the current funding line.

For future Prioritized List with back line changes

GUIDELINE NOTE 92, ACUPUNCTURE

Lines 1, 20~~7~~8, ~~374,~~ 407, 41~~4~~5, 46~~8~~7, ~~545,~~ 54~~6~~3

Inclusion of acupuncture (CPT 97810-97814) on the Prioritized List has the following limitations:

Line 1 PREGNANCY

Acupuncture pairs on Line 1 for the following conditions and codes.

Hyperemesis gravidarum

ICD-10-CM code: O21.0, O21.1

Acupuncture pairs with hyperemesis gravidarum when a diagnosis is made by the maternity care provider and referred for acupuncture treatment for up to ~~2~~ 12 sessions of acupressure/acupuncture.

Breech presentation

ICD-10-CM code: O32.1xx0, O32.8xx0

Acupuncture (and moxibustion) is paired with breech presentation when a referral with a diagnosis of breech presentation is made by the maternity care provider, the patient is between 33 and 38 weeks gestation, for up to ~~2~~ 12 visits.

Back and pelvic pain of pregnancy

ICD-10-CM code: O33.0

Acupuncture is paired with back and pelvic pain of pregnancy when referred by maternity care provider/primary care provider for up to 12 sessions.

Line 20~~7~~8 DEPRESSION AND OTHER MOOD DISORDERS, MILD OR MODERATE

Acupuncture is paired with the treatment of post-stroke depression only. Treatments may be billed to a maximum of 30 minutes face-to-face time and limited to ~~15~~ 12 total sessions, with documentation of meaningful improvement.

~~Line 374 DISORDERS OF SPINE WITH NEUROLOGIC IMPAIRMENT~~

~~Acupuncture is included on Line 374 only for pairing with disorders of the spine with myelopathy and/or radiculopathy represented by the diagnosis codes G83.4, M47.1x, M47.2x, M50.0x, M50.1x, M51.0x, M51.1x, M54.1x) with referral, for up to 12 sessions.~~

Line 407 CONDITIONS OF THE BACK AND SPINE

Acupuncture is included on line 407 for pairing with visit limitations as in **GUIDELINE NOTE XXX NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE**

Line 414~~4~~5 MIGRAINE HEADACHES

Acupuncture pairs on Line 414~~4~~5 for ~~G43.9~~ Migraine (ICD-10-CM code G43.0xx, G43.1xx, G43.5xx, G43.7xx, G43.8xx, G43.9xx)~~, when referred,~~ for up to 12 sessions.

Line 46~~8~~7 OSTEOARTHRITIS AND ALLIED DISORDERS

Acupuncture pairs on Line 46~~8~~7 for osteoarthritis of the knee only (ICD-10 code M17.xx)~~, when referred,~~ for up to 12 sessions.

~~*Line 545 ACUTE AND CHRONIC DISORDERS OF SPINE WITHOUT NEUROLOGIC IMPAIRMENT~~

~~Acupuncture pairs on Line 545 with the low back diagnoses (ICD-10-CM codes G83.4, M47.1x, M47.2x, M50.0x, M50.1x, M51.1x, M54.1x, M51.36, M51.86, M54.5, M99.03,S33.5xxx, S33.9xxx, S39.092x,S39.82xx, S39.92xx), when referred, for up to 12 sessions. Acupuncture pairs with chronic (>90 days) neck pain diagnoses (ICD-10-CM M53.82, M54.2, S13.4XXX, S13.8XXX), when referred, for up to 12 sessions.~~

*Line 54~~6~~3 TENSION HEADACHES

Acupuncture is included on Line 54~~6~~3 for treatment of tension headaches (ICD-10-CM G44.2x)~~, when referred,~~ for up to 12 sessions.

The development of this guideline note was informed by a HERC evidence-based guideline. See http://www.oregon.gov/oha/herc/Pages/blog-low-back-non-pharmacologic-intervention.aspx

*Below the current funding line.

Tobacco cessation coverage and prevention

Question: Should the guideline on tobacco cessation coverage be modified?

Question source: HERC Staff, Public Health Division

Issue: Currently, there is a wide variety in coverage by CCOs and DMAP for tobacco cessation. Some are covering quit attempts once in a lifetime, others are covering more frequently, and prior authorizations are variable.

Several years ago, a statewide collaborative developed a plan in Oregon to increase quit attempts and reduce smoking rates, named Helping Benefit Oregon Smokers collaborative. The Public Health Division continues work on this area identifying the services most helpful in improving quit rates and translating the new requirements based on the ACA mandate. The ACA mandates smoking cessation coverage. However, not all CCOs are currently offering the ACA required level of coverage.

Several strategies are evidence-based to assist in smoking cessation, both pharmacologic and behavioral. Pharmacologic strategies include nicotine replacement therapy (NRT), bupropion (Zyban), nortriptyline, and varenicline (Chantix). Group and individual counseling, in person and telephonic are all considered effective. And acupuncture and hypnosis have been proposed as beneficial for smoking cessation. A number of public health strategies are evidence based to both prevent initiation of smoking and assist with smoking cessation.

Recently, the Tobacco Cessation Services report was released that addressed benefit coverage by the CCOs and FFS. They found that in general just over half of smokers were encouraged by their providers to quit in the last 6 months. All CCOs use prior authorization for at least one of the pharmaceutical products. Some CCOS have done targeted strategies for high risk populations such as incentives, additional services, and information for pregnant women who smoke. Two CCOs have tobacco free campuses.

Prioritized List Status

Line: 5

Condition:	TOBACCO DEPENDENCE (See Guideline Notes 4,64,65)
Treatment:	MEDICAL THERAPY/BRIEF COUNSELING NOT TO EXCEED 10 FOLLOW-UP VISITS OVER 3 MONTHS
ICD-9:	305.1,649.00-649.04
CPT:	96127-96154,97810-97814,98966-98969,99078,99201-99215,99224,99324-99350, 99366,99406,99407,99441-99449,99487-99498,99605-99607
HCPCS:	D1320,G0425-G0427,G0436,G0437,G0459,G0463,G0466,G0467,G0469,G0470, G9016,H0038,S9075,S9453

GUIDELINE NOTE 4, TOBACCO DEPENDENCE

Line 5

Persons are eligible for tobacco dependence counseling if a documented quit date has been established.

Tobacco cessation coverage and prevention

GUIDELINE NOTE 106, PREVENTIVE SERVICES

Line 3

Included on this line are the following preventive services:

1. US Preventive Services Task Force (USPSTF) "A" and "B" Recommendations (as of May 2012):
   http://www.uspreventiveservicestaskforce.org/Page/Name/uspstf-a-and-b-recommendations/
2. American Academy of Pediatrics (AAP) Bright Futures Guidelines (published 2008):
   http://brightfutures.aap.org/pdfs/Guidelines_PDF/20-Appendices_PeriodicitySchedule.pdf
3. Health Resources and Services Administration (HRSA) Women's Preventive Services - Required Health Plan Coverage Guidelines: (approved with Affordable Care Act on March 23, 2010)
   http://www.hrsa.gov/womensguidelines/
4. Immunizations as recommended by the Advisory Committee on Immunization Practices (ACIP) and approved for the Oregon Immunization Program:
   http://public.health.oregon.gov/PreventionWellness/VaccinesImmunization/ImmunizationProviderResources/Documents/DMAPvactable.pdf

Tobacco cessation coverage and prevention

Evidence Summary:

1) **Cahill 2013**, Cochrane review of pharmacological interventions for smoking cessation
    a. 12 reviews, with 267 studies/101,804 patients
    b. Both nicotine replacement therapy (NRT) and bupropion were superior to placebo (odds ratios (OR) 1.84; 95% credible interval (CredI) 1.71 to 1.99, and 1.82; 95% CredI 1.60 to 2.06 respectively). Head-to-head comparisons between bupropion and NRT showed equal efficacy (OR 0.99; 95% CredI 0.86 to 1.13).
    c. Varenicline increased the odds of quitting compared with placebo (OR 2.88; 95% CredI 2.40 to 3.47). Varenicline was superior to single forms of NRT (OR 1.57; 95% CredI 1.29 to 1.91), and to bupropion (OR 1.59; 95% CredI 1.29 to 1.96). Varenicline was more effective than nicotine patch (OR 1.51; 95% CredI 1.22 to 1.87), than nicotine gum (OR 1.72; 95% CredI 1.38 to 2.13), and than 'other' NRT (inhaler, spray, tablets, lozenges; OR 1.42; 95% CredI 1.12 to 1.79), but was not more effective than combination NRT (OR 1.06; 95% CredI 0.75 to 1.48).
    d. Across the 82 included and excluded bupropion trials, our estimate of six seizures in the bupropion arms versus none in the placebo arms was lower than the expected rate (1:1000), at about 1:1500. SAE meta-analysis of the bupropion studies demonstrated no excess of neuropsychiatric (RR 0.88; 95% CI 0.31 to 2.50) or cardiovascular events (RR 0.77; 95% CI 0.37 to 1.59). SAE meta-analysis of 14 varenicline trials found no difference between the varenicline and placebo arms (RR 1.06; 95% CI 0.72 to 1.55), and subgroup analyses detected no significant excess of neuropsychiatric events (RR 0.53; 95% CI 0.17 to 1.67), or of cardiac events (RR 1.26; 95% CI 0.62 to 2.56).
    a. Nortriptyline increased the chances of quitting (RR 2.03; 95% CI 1.48 to 2.78). Neither nortriptyline nor bupropion were shown to enhance the effect of NRT compared with NRT alone
    b. **Authors' conclusions** NRT, bupropion, varenicline and cytisine have been shown to improve the chances of quitting. Combination NRT and varenicline are equally effective as quitting aids. Nortriptyline also improves the chances of quitting. On current evidence, none of the treatments appear to have an incidence of adverse events that would mitigate their use.
2) **Hughes 2014,** Cochrane review of antidepressants for smoking cessation
    a. 65 trials of bupropion, 10 trials of nortiptyline
    b. There was high quality evidence that, when used as the sole pharmacotherapy, bupropion significantly increased long-term cessation (44 trials, N = 13,728, risk ratio [RR] 1.62, 95% confidence interval [CI] 1.49 to 1.76). There was moderate quality evidence, limited by a relatively small number of trials and participants, that nortriptyline also significantly increased long-term cessation when used as the sole pharmacotherapy (six trials, N = 975, RR 2.03, 95% CI 1.48 to 2.78). There is insufficient evidence that adding bupropion (12 trials, N = 3487, RR 1.9, 95% CI 0.94 to 1.51) or nortriptyline (4 trials, N = 1644, RR 1.21, 95% CI 0.94 to 1.55) to nicotine replacement therapy (NRT) provides an additional long-term benefit.
    c. There is a risk of about 1 in 1000 of seizures associated with bupropion use. Bupropion has been associated with suicide risk, but whether this is causal is unclear. Nortriptyline has the potential for serious side-effects, but none have been seen in the few small trials for smoking cessation.

   d. **Authors' conclusions** The antidepressants bupropion and nortriptyline aid long-term smoking cessation. Adverse events with either medication appear to rarely be serious or lead to stopping medication. Evidence suggests that the mode of action of bupropion and nortriptyline is independent of their antidepressant effect and that they are of similar efficacy to nicotine replacement. Reuptake inhibitors (e.g. fluoxetine) nor monoamine oxidase inhibitors aid cessation.

3) **Stead 2012,** Cochrane review of NRT for smoking cessation (not included in packet due to study's length)
   a. N=150 trials (>50,000 participants)
   b. The risk ratio (RR) of abstinence for any form of NRT relative to control was 1.60 (95% confidence interval [CI] 1.53 to 1.68). The pooled RRs for each type were 1.49 (95% CI 1.40 to 1.60, 55 trials) for nicotine gum; 1.64 (95% CI 1.52 to 1.78, 43 trials) for nicotine patch; 1.95 (95% CI 1.61 to 2.36, 6 trials) for oral tablets/lozenges; 1.90 (95% CI 1.36 to 2.67, 4 trials) for nicotine inhaler; and 2.02 (95% CI 1.49 to 2.73, 4 trials) for nicotine nasal spray. One trial of oral spray had an RR of 2.48 (95% CI 1.24 to 4.94). The effects were largely independent of the duration of therapy, the intensity of additional support provided or the setting in which the NRT was offered.
   c. Five studies directly compared NRT to a non-nicotine pharmacotherapy, bupropion; there was no evidence of a difference in efficacy (RR 1.01; 95% CI 0.87 to 1.18). A combination of NRT and bupropion was more effective than bupropion alone (RR 1.24; 95% CI 1.06 to 1.45, 4 trials). Adverse effects from using NRT are related to the type of product, and include skin irritation from patches and irritation to the inside of the mouth from gum and tablets. There is no evidence that NRT increases the risk of heart attacks.
   d. **Authors' conclusions** All of the commercially available forms of NRT (gum, transdermal patch, nasal spray, inhaler and sublingual tablets/lozenges) can help people who make a quit attempt to increase their chances of successfully stopping smoking. NRTs increase the rate of quitting by 50 to 70%, regardless of setting. The effectiveness of NRT appears to be largely independent of the intensity of additional support provided to the individual.

4) **White 2014,** Cochrane review of acupuncture for smoking cessation
   a. N=38 studies
      i. N=3 studies (393 patients) comparing acupuncture to waiting list control
      ii. N=19 studies (1,588 patients) comparing active acupuncture to sham acupuncture
   a. Based on three studies, acupuncture was not shown to be more effective than a waiting list control for long-term abstinence, with wide confidence intervals and evidence of heterogeneity (n = 393, risk ratio [RR] 1.79, 95% confidence interval [CI] 0.98 to 3.28, I^2 = 57%). Compared with sham acupuncture, the RR for the short-term effect of acupuncture was 1.22 (95% CI 1.08 to 1.38), and for the long-term effect was 1.10 (95% CI 0.86 to 1.40). Acupuncture was less effective than nicotine replacement therapy (NRT). There was no evidence that acupuncture is superior to psychological interventions in the short- or long-term.
   b. Moderate quality of evidence of no long term benefit for acupuncture on smoking cessation, although evidence of short term effect

c. **Authors' conclusions** Although pooled estimates suggest possible short-term effects there is no consistent, bias-free evidence that acupuncture, acupressure, or laser therapy have a sustained benefit on smoking cessation for six months or more. However, lack of evidence and methodological problems mean that no firm conclusions can be drawn.

5) **Stead 2009,** Cochrane review of group therapy for smoking cessation
   a. N=53 trials
   b. There was an increase in cessation with the use of a group programme (N = 4375, relative risk (RR) 1.98, 95% confidence interval (CI) 1.60 to 2.46). There was statistical heterogeneity between trials in the comparison of group programmes with no intervention controls so we did not estimate a pooled effect. We failed to detect evidence that group therapy was more effective than a similar intensity of individual counselling. There was limited evidence that the addition of group therapy to other forms of treatment, such as advice from a health professional or nicotine replacement, produced extra benefit. Programmes which included components for increasing cognitive and behavioural skills were not shown to be more effective than same length or shorter programmes without these components.
   c. **Authors' conclusions** Group therapy is better for helping people stop smoking than self help, and other less intensive interventions. There is not enough evidence to evaluate whether groups are more effective, or cost-effective, than intensive individual counselling. There is not enough evidence to support the use of particular psychological components in a programme beyond the support and skills training normally included.

6) Civljak, 2013, Cochrane review of internet based interventions of smoking cessation
   a. N= 28 studies with > 45,000 participants
   b. **Results:** pooled results from three trials that compared interactive and individually tailored interventions to usual care or written self help detected a statistically significant effect in favour of the intervention (RR 1.48, 95% CI 1.11 to 2.78). However all three trials were judged to be at high risk of bias in one domain and high statistical heterogeneity was detected (I^2 = 53%), with no obvious clinical explanation. Pooled results fromtwo studies of an interactive, tailored intervention involving the Internet and automated phone contacts also detected a significant effect (RR 2.05, 95%CI 1.42 to 2.97, I^2 = 42%).
   c. **Conclusions** Results suggest that some Internet-based interventions can assist smoking cessation at six months or longer, particularly those which are interactive and tailored to individuals. However, the trials that compared Internet interventions with usual care or self help did not show consistent effects and were at risk of bias.

7) Community Preventive Services Task Force, 2012, Systematic review of telephonic quit lines
   a. 72 studies total, 60 of which evaluated proactive counseling
   b. Economic analysis: based on 27 studies
      i. Cost-effectiveness of providing quitline counseling and cessation information: median estimate of $2,012 per quality-adjusted life year (QALY) saved (range of values: $439/QALY to $2,627/QALY; 6 studies)

ii. Cost-effectiveness of adding cessation medications to existing quitline services: median estimate $795 per QALY saved (range of values: $272/QALY to $4,110/QALY; 6 studies)
iii. Cost-effectiveness of providing a combination of quitline counseling, nicotine replacement therapy (NRT), and media promotion: $7,813 per QALY saved (1 study)

c. Conclusions: quitline services are cost-effective and recommended.

8) **USPSTF, 2015 (non-pregnant adults)**
   a. The USPSTF recommends that clinicians ask all adults about tobacco use, advise them to stop using tobacco, and provide behavioral interventions and U.S. Food and Drug Administration (FDA)–approved pharmacotherapy for cessation to adults who use tobacco.
      i. GRADE A Recommendation
   b. The USPSTF concludes that the current evidence is insufficient to recommend electronic nicotine delivery systems (ENDS) for tobacco cessation in adults, including pregnant women. The USPSTF recommends that clinicians direct patients who smoke tobacco to other cessation interventions with established effectiveness and safety (previously stated).
      i. GRADE I Recommendation
9) **Barnes, 2010,** Cochrane systematic review of RCTs on hypnotherapy for smoking cessation
   a. 11 RCTs comparing hypnotherapy to controls (no treatment, advice, or psychological treatment)
   b. Results: significant heterogeneity of results
   c. Conclusions: We have not shown that hypnotherapy has a greater effect on six-month quit rates than other interventions or no treatment. There is not enough evidence to show whether hypnotherapy could be as effective as counselling treatment. The effects of hypnotherapy on smoking cessation claimed by uncontrolled studies were not confirmed by analysis of randomized controlled trials.

<u>Cost effectiveness analysis</u>

1) Richard, 2012
   a. Massachusetts Medicaid invested in a comprehensive tobacco program
   b. Cost benefit analysis to evaluate return on investment
   c. Program costs included pharmacotherapy, counseling and outreach costs
   d. Costs per program participant: $183
   e. Inpatient savings per participant $571
   f. ROI: Every $1 in program costs was associated with $3.12 (range $3.00 to $3.25) in medical savings, for a $2.12 (range $2.00 to $2.25) return on investment to the Medicaid program for every dollar spent.

<u>ACA requirements (as interpreted by Oregon Public Health Division)</u>

- Under Section 4107 of the Affordable Care Act, all state Medicaid programs are required to provide a comprehensive tobacco cessation benefit (as defined by the US Public

Health Service guidelines) to pregnant women who are enrolled in Medicaid, effective October 2010.

- As of January 2014, Section 2502 of the law bars state Medicaid programs from excluding cessation medications, including over-the-counter medications, from coverage for pregnant women.

- In 2014, the Department of Health and Human Services clarified what constitutes a comprehensive tobacco cessation benefit under the ACA. The benefit must include no cost-sharing, screening for tobacco use and tobacco cessation services for those who use tobacco products. The guidance defines an appropriate benefit as:

    - Four tobacco counseling sessions of at least 10 minutes each (including telephone, group and/or individual counseling),
    - All medications approved by the FDA as safe and effective for smoking cessation,
    - Benefits should be accessible at least twice a year to tobacco users, recognizing not everyone quits on their first try,
    - Plans should not require prior authorization to access these benefits.
    - Cessation benefits shall be provided at no cost to the patient. No copays, coinsurance or deductibles should be charged.

The Affordable Care Act requires coverage for smoking cessation. The FAQ[1] additionally states coverage is mandated for:

> All Food and Drug Administration (FDA)-approved tobacco cessation medications (including both prescription and over-the-counter medications) for a 90-day treatment regimen, without prior authorization, when prescribed by a health care provider.

[1] http://www.dol.gov/ebsa/faqs/faq-aca19.html

National picture

1) MMWR, 2015
2) Review of coverage policy of all 50 states Medicaid agencies
3) 9 currently have full coverage without barriers
4) Oregon's variability means that it is not one of the 9
5) Evidence of benefit from more comprehensive tobacco coverage policies in Medicaid, associated with more successful quit rates.

Oregon Public Health Division

1) A Guide for CCOs on evidence based strategies https://public.health.oregon.gov/PreventionWellness/TobaccoPrevention/Documents/evidence-based_strategies_reduce_tob_use_guide_cco.pdf (not included in packet due to study's length)
    a. Plan level steps to Identify tobacco users

b. Encourage and incentivize providers to ask about and document tobacco use
c. Offer comprehensive cessation benefits
d. Eliminate barriers to accessing treatment
e. Pro-actively reach out to all identified tobacco users to encourage them to quit or take advantage of their benefits.
f. Ensure your provider network is aware of the existing benefits
g. Provide tobacco-related trainings to contracted providers
h. Systematically embed referral systems in clinic work-flows and electronic health records
i. Adopt and Implement a Tobacco-Free Campus Policy
j. Work with local partners
k. Communicate and outreach to members from special population groups, including those known to use tobacco at higher rates

2) Multisectoral interventions one pager - take home points:
    a. Conducting simultaneous multi-sector interventions maximizes the health and economic benefits of addressing tobacco use. Every dollar spent on coordinated, evidence-based tobacco control efforts can yield a savings of $55. Coordinated efforts are effective across racial and ethnic groups, education levels, and levels of socioeconomic status.

<u>CDC Community Guide to Preventive Services</u>

1) Evidence-based recommendations for effective community services
2) Based on high quality systematic reviews
3) Fall into rubric of:
    a. Reducing tobacco use initiation
    b. Increasing tobacco use cessation
    c. Reducing exposure to second-hand tobacco smoke
    d. Restricting minors' access to tobacco products
    e. Decreasing tobacco use among workers

Tobacco cessation coverage and prevention

TASK FORCE FINDINGS ON TOBACCO USE

The Community Preventive Services Task Force (Task Force) has released the following findings on what works in public health to prevent tobacco use. These findings are compiled in The Guide to Community Preventive Services (The Community Guide) and listed in the table below. Use the findings to identify strategies and interventions you could use for your community.

Legend for Task Force Findings: ● Recommended ◆ Insufficient Evidence ▲ Recommended Against (See reverse for detailed descriptions.)

Intervention	Task Force Finding
Reducing Tobacco Use Initiation	
Increasing the unit price of tobacco products	●
Mass media campaigns when combined with other interventions	●
Smoke-free policies	●
Increasing Tobacco Use Cessation	
Increasing the unit price of tobacco products	●
Mass media campaigns when combined with other interventions	●
Mass-reach health communication interventions	●
Mobile phone-based interventions	●
Multicomponent interventions that include client telephone support	●
Smoke-free policies	●
Provider reminders when used alone	●
Provider reminders with provider education	●
Reducing client out-of-pocket costs for cessation therapies	●
Internet-based interventions	◆
Mass media – cessation contests	◆
Mass media – cessation series	◆
Provider assessment and feedback	◆
Provider education when used alone	◆

Intervention	Task Force Finding
Reducing Exposure to Environmental Tobacco Smoke	
Smoke-free policies	●
Community education to reduce exposure in the home	◆
Restricting Minors' Access to Tobacco Products	
Community mobilization with additional interventions	●
Sales laws directed at retailers when used alone	◆
Active enforcement of sales laws directed at retailers when used alone	◆
Community education about youth's access to tobacco products when used alone	◆
Retailer education with reinforcement and information on health consequences when used alone	◆
Retailer education without reinforcement when used alone	◆
Laws directed at minors' purchase, possession, or use of tobacco products when used alone	◆
Decreasing Tobacco Use Among Workers	
Smoke-free policies	●
Incentives and competitions to increase smoking cessation combined with additional interventions	●
Incentives and competitions to increase smoking cessation when used alone	◆

Visit the "Tobacco Use" page of The Community Guide website at www.thecommunityguide.org/tobacco to find summaries of Task Force findings and recommendations on tobacco use. Click on each topic area to find results from the systematic reviews, included studies, evidence gaps, and journal publications.

The Centers for Disease Control and Prevention provides administrative, research, and technical support for the Community Preventive Services Task Force.

Tobacco cessation coverage and prevention

HERC Staff Assessment:
Currently there is inconsistency among CCOs and Fee-for-service (FFS) for coverage of smoking cessation.

Nicotine replacement therapy (NRT), bupropion, varenicline, and nortriptyline are effective for smoking cessation. Group therapy is better than self-help and other less intensive interventions. Telephonic quit line counseling is cost-effective. Individually tailored and interactive internet based strategies are likely effective.

There is insufficient evidence that hypnosis is effective. There is insufficient evidence that acupuncture is effective, or as effective as other tobacco cessation aids.

There are a number of evidence-based strategies outside of the typical health care setting that are effective at reducing incidence of tobacco dependence and reducing smoking prevalence. Some CCOs are already doing community-based interventions, and in 2016, a tobacco use prevalence measure, available to CCOs that meet criteria for their tobacco cessation benefit, will become a new incentive metric. Detailing available evidence-based interventions could assist CCOs and Health Systems Division (historically MAP) in identifying interventions of interest to try to reduce tobacco use prevalence and achieve their 2016 metric goals.

There is currently not a clear place on the Prioritized List to address interventions that fall outside of the immediate clinical-coding-based encounter. Adding a new section to the Prioritized List that captures "Multisector Interventions" would allow for addressing of evidence-based interventions that would be useful to plans.

HERC Staff Recommendations:

1) Modify Guideline Note 4 as follows:

GUIDELINE NOTE 4, TOBACCO DEPENDENCE

Line 5

~~Persons are eligible for tobacco dependence counseling if a documented quit date has been established.~~ Pharmacotherapy and behavioral counseling are included on this line, alone or in combination, for at least 2 quit attempts per year. A minimum of four counseling sessions of at least 10 minutes each (group or individual, telephonic or in person) are included for each quit attempt. More intensive interventions and group therapy are likely to be the most effective behavioral interventions.

Inclusion on this line follows the minimum standard criteria as defined in the Oregon Public Health Division "Standard Tobacco Cessation Coverage" based on the ACA, available here:

https://public.health.oregon.gov/PreventionWellness/TobaccoPrevention/Pages/pubs.aspx

Tobacco cessation coverage and prevention

2) Add a Tobacco prevention and cessation MULTISECTOR INTERVENTIONS STATEMENT

a. MULTISECTOR INTERVENTIONS 1, TOBACCO PREVENTION AND CESSATION

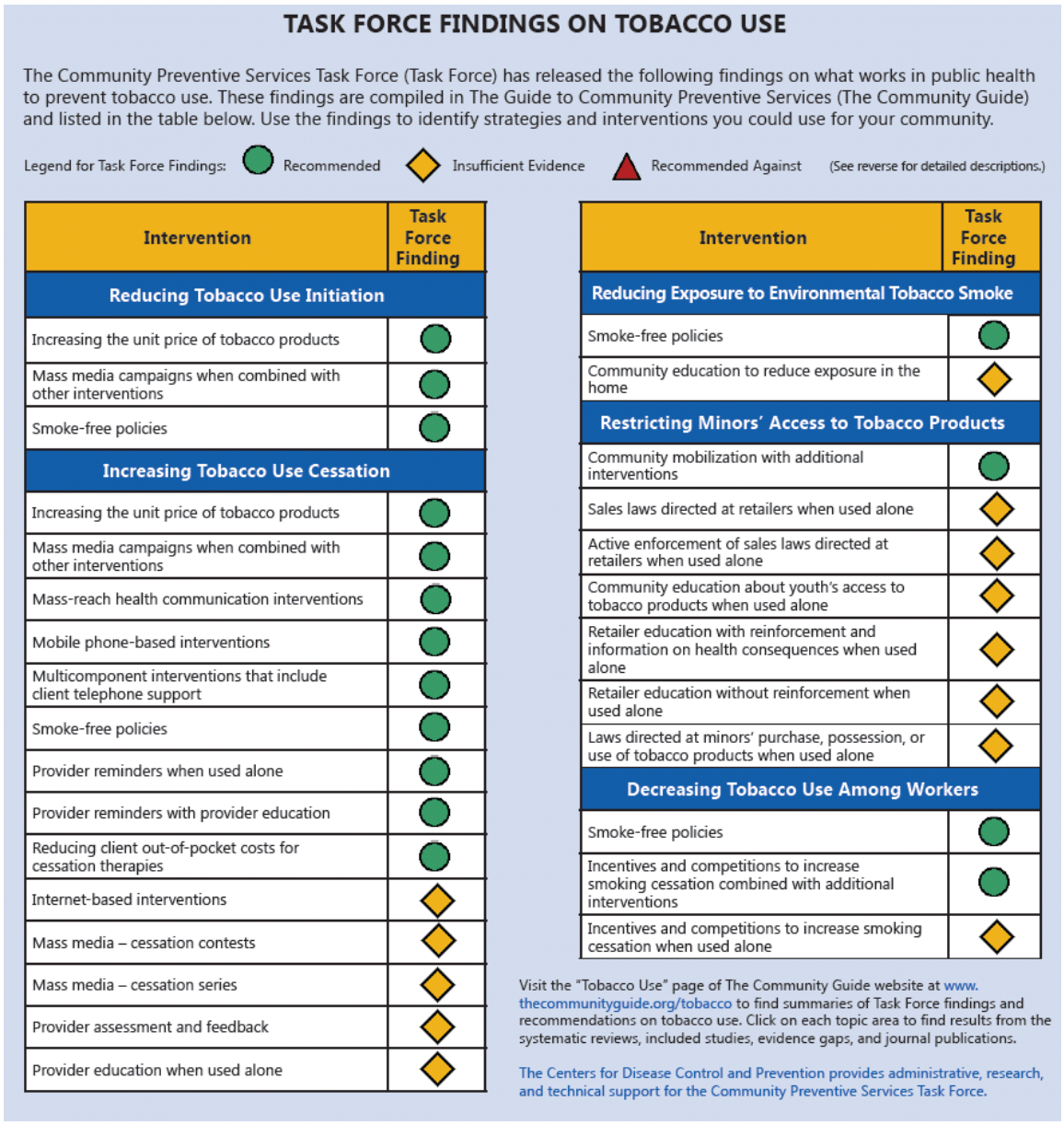
Benefit coverage for smoking cessation on Line 5 and in GUIDELINE NOTE 4, *TOBACCO DEPENDENCE* is intended to be offered with minimal barriers, in order to encourage utilization. To further prevent tobacco use and help people quit, additional evidence-based policy and programmatic interventions from a population perspective are available here:

- Oregon Public Health Division's Health Promotion and Chronic Disease Prevention Section: Evidence-Based Strategies for Reducing Tobacco Use A Guide for CCOs https://public.health.oregon.gov/PreventionWellness/TobaccoPrevention/Documents/evidence-based_strategies_reduce_tob_use_guide_cco.pdf

- Community Preventive Services Task Force (supported by the CDC) - What Works: Tobacco Use http://www.thecommunityguide.org/about/What-Works-Tobacco-factsheet-and-insert.pdf

The Community Preventive Services Task Force identified the following evidence-based strategies:

Tobacco cessation coverage and prevention



TASK FORCE FINDINGS ON TOBACCO USE

The Community Preventive Services Task Force (Task Force) has released the following findings on what works in public health to prevent tobacco use. These findings are compiled in The Guide to Community Preventive Services (The Community Guide) and listed in the table below. Use the findings to identify strategies and interventions you could use for your community.

Legend for Task Force Findings: Recommended; Insufficient Evidence; Recommended Against (See reverse for detailed descriptions.)

Intervention	Task Force Finding
Reducing Tobacco Use Initiation	
Increasing the unit price of tobacco products	Recommended
Mass media campaigns when combined with other interventions	Recommended
Smoke-free policies	Recommended
Increasing Tobacco Use Cessation	
Increasing the unit price of tobacco products	Recommended
Mass media campaigns when combined with other interventions	Recommended
Mass-reach health communication interventions	Recommended
Mobile phone-based interventions	Recommended
Multicomponent interventions that include client telephone support	Recommended
Smoke-free policies	Recommended
Provider reminders when used alone	Recommended
Provider reminders with provider education	Recommended
Reducing client out-of-pocket costs for cessation therapies	Recommended
Internet-based interventions	Insufficient Evidence
Mass media – cessation contests	Insufficient Evidence
Mass media – cessation series	Insufficient Evidence
Provider assessment and feedback	Insufficient Evidence
Provider education when used alone	Insufficient Evidence

Intervention	Task Force Finding
Reducing Exposure to Environmental Tobacco Smoke	
Smoke-free policies	Recommended
Community education to reduce exposure in the home	Insufficient Evidence
Restricting Minors' Access to Tobacco Products	
Community mobilization with additional interventions	Recommended
Sales laws directed at retailers when used alone	Insufficient Evidence
Active enforcement of sales laws directed at retailers when used alone	Insufficient Evidence
Community education about youth's access to tobacco products when used alone	Insufficient Evidence
Retailer education with reinforcement and information on health consequences when used alone	Insufficient Evidence
Retailer education without reinforcement when used alone	Insufficient Evidence
Laws directed at minors' purchase, possession, or use of tobacco products when used alone	Insufficient Evidence
Decreasing Tobacco Use Among Workers	
Smoke-free policies	Recommended
Incentives and competitions to increase smoking cessation combined with additional interventions	Recommended
Incentives and competitions to increase smoking cessation when used alone	Insufficient Evidence

Visit the "Tobacco Use" page of The Community Guide website at www.thecommunityguide.org/tobacco to find summaries of Task Force findings and recommendations on tobacco use. Click on each topic area to find results from the systematic reviews, included studies, evidence gaps, and journal publications.

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3) Rename treatment description

Line: 5

Condition: TOBACCO DEPENDENCE (See Guideline Notes 4,64,65)

Treatment: MEDICAL THERAPY/~~BRIEF~~ BEHAVIORAL COUNSELING ~~NOT TO EXCEED 10 FOLLOW-UP VISITS OVER 3 MONTHS~~

4) Continue to not cover hypnosis for smoking cessation (on the Recommended for noncovered services table)

[Intervention Review]

Hypnotherapy for smoking cessation

Jo Barnes[1], Christine Y Dong[1], Hayden McRobbie[2], Natalie Walker[3], Monaz Mehta[4], Lindsay F Stead[4]

[1]School of Pharmacy, University of Auckland, Auckland, New Zealand. [2]UK Centre for Tobacco Control Studies, Wolfson Institute of Preventive Medicine, Barts & The London School of Medicine and Dentistry, Queen, London, UK. [3]Clinical Trials Research Unit, University of Auckland, Auckland, New Zealand. [4]Department of Primary Health Care, University of Oxford, Oxford, UK

Contact address: Jo Barnes, School of Pharmacy, University of Auckland, Private Bag 92019, Grafton Campus, Auckland, New Zealand. j.barnes@auckland.ac.nz.

Editorial group: Cochrane Tobacco Addiction Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 10, 2010.
Review content assessed as up-to-date: 21 July 2010.

Citation: Barnes J, Dong CY, McRobbie H, Walker N, Mehta M, Stead LF. Hypnotherapy for smoking cessation. *Cochrane Database of Systematic Reviews* 2010, Issue 10. Art. No.: CD001008. DOI: 10.1002/14651858.CD001008.pub2.

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ABSTRACT

Background

Hypnotherapy is widely promoted as a method for aiding smoking cessation. It is proposed to act on underlying impulses to weaken the desire to smoke or strengthen the will to stop.

Objectives

To evaluate the efficacy of hypnotherapy for smoking cessation.

Search methods

We searched the Cochrane Tobacco Addiction Group Specialized Register and the databases MEDLINE, EMBASE, AMED, SCI, SSCI using the terms smoking cessation and hypnotherapy or hypnosis. Date of most recent searches July 2010. There were no language restrictions.

Selection criteria

We considered randomized controlled trials of hypnotherapy which reported smoking cessation rates at least six months after the beginning of treatment.

Data collection and analysis

Three authors independently extracted data on participant characteristics, the type and duration of the hypnotherapy, the nature of the control group, smoking status, method of randomization, and completeness of follow up. They also independently assessed the quality of the included studies.

The main outcome measure was abstinence from smoking after at least six months follow up. We used the most rigorous definition of abstinence in each trial, and biochemically validated rates where available. Those lost to follow up were considered to be smoking. We summarised effects as risk ratios (RR). Where possible, we performed meta-analysis using a fixed-effect model. We also noted any adverse events reported.

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[Overview of Reviews]

Pharmacological interventions for smoking cessation: an overview and network meta-analysis

Kate Cahill[1], Sarah Stevens[1], Rafael Perera[1], Tim Lancaster[1]

[1]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

Contact address: Kate Cahill, Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG, UK. kate.cahill@phc.ox.ac.uk.

Editorial group: Cochrane Tobacco Addiction Group.
Publication status and date: Edited (no change to conclusions), published in Issue 7, 2015.
Review content assessed as up-to-date: 16 November 2012.

Citation: Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database of Systematic Reviews* 2013, Issue 5. Art. No.: CD009329. DOI: 10.1002/14651858.CD009329.pub2.

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ABSTRACT

Background

Smoking is the leading preventable cause of illness and premature death worldwide. Some medications have been proven to help people to quit, with three licensed for this purpose in Europe and the USA: nicotine replacement therapy (NRT), bupropion, and varenicline. Cytisine (a treatment pharmacologically similar to varenicline) is also licensed for use in Russia and some of the former socialist economy countries. Other therapies, including nortriptyline, have also been tested for effectiveness.

Objectives

How do NRT, bupropion and varenicline compare with placebo and with each other in achieving long-term abstinence (six months or longer)?

How do the remaining treatments compare with placebo in achieving long-term abstinence?

How do the risks of adverse and serious adverse events (SAEs) compare between the treatments, and are there instances where the harms may outweigh the benefits?

Methods

The overview is restricted to Cochrane reviews, all of which include randomised trials. Participants are usually adult smokers, but we exclude reviews of smoking cessation for pregnant women and in particular disease groups or specific settings. We cover nicotine replacement therapy (NRT), antidepressants (bupropion and nortriptyline), nicotine receptor partial agonists (varenicline and cytisine), anxiolytics, selective type 1 cannabinoid receptor antagonists (rimonabant), clonidine, lobeline, dianicline, mecamylamine, Nicobrevin, opioid antagonists, nicotine vaccines, and silver acetate. Our outcome for benefit is continuous or prolonged abstinence at least six months from the start of treatment. Our outcome for harms is the incidence of serious adverse events associated with each of the treatments.

We searched the Cochrane Database of Systematic Reviews (CDSR) in *The Cochrane Library*, for any reviews with 'smoking' in the title, abstract or keyword fields. The last search was conducted in November 2012. We assessed methodological quality using a revised version of the AMSTAR scale. For NRT, bupropion and varenicline we conducted network meta-analyses, comparing each with the others and with placebo for benefit, and varenicline and bupropion for risks of serious adverse events.

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www.thecommunityguide.org

The Guide to Community Preventive Services
THE COMMUNITY GUIDE
What Works to Promote Health

WHAT WORKS

Tobacco Use

Evidence-Based Interventions for Your Community



Tobacco use is a leading cause of preventable death and disability nationwide, costing the United States billions of dollars in lost productivity and health care expenses. This brochure is designed to help public health program planners, community advocates, educators, and policymakers find proven interventions - including programs, services, and policies - for reducing tobacco use. It can help decision makers in both public and private sectors make choices about what interventions are best for their communities.

This brochure summarizes information in The Guide to Community Preventive Services (The Community Guide), an essential resource for people who want to know what works in public health.. Use this information to select interventions you can adapt for your community to:

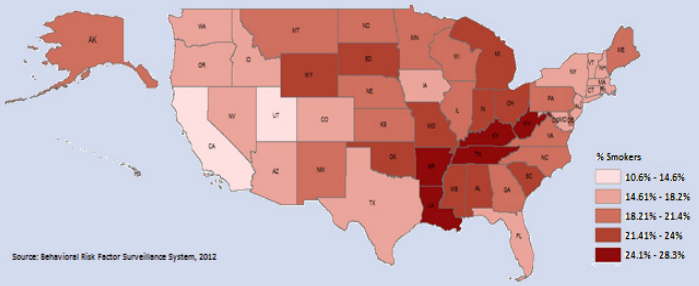
- Prevent people from starting to smoke
- Help people quit using tobacco products of all types
- Reduce people's exposure to secondhand smoke
- Keep minors from obtaining tobacco products
- Decrease tobacco use in the workplace

The Community Guide provides evidence-based findings and recommendations from the Community Preventive Services Task Force (Task Force) about community preventive services, programs, and policies to improve health. Learn more about The Community Guide and what works to control tobacco use by visiting www.thecommunityguide.org/tobacco.

The Centers for Disease Control and Prevention provides administrative, research, and technical support for the Community Preventive Services Task Force.

THE PUBLIC HEALTH CHALLENGE

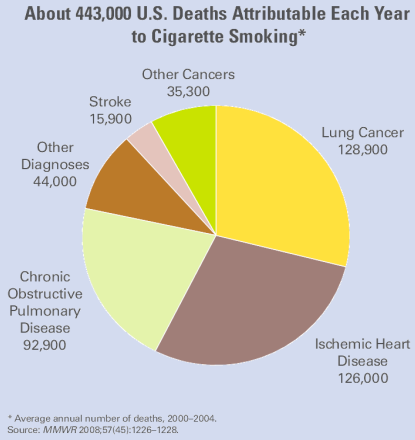
Tobacco use by the numbers



- Nearly **44 million adults** - about 19 percent - smoke cigarettes[3]
- More than **80 percent** started smoking before age 18[4]
- **90 million** nonsmokers are exposed to secondhand smoke[6]
- States in the **Midwest and Southeast** have the most smokers[3]
- **3.5 percent of adults and 5.5 percent of 18-25 year olds** who currently use tobacco, use smokeless tobacco[7]

For more information on tobacco use in the U.S., including state-by-state data, see www.cdc.gov/tobacco/data_statistics.

Cigarette smoking takes a toll



- Each year in the U.S., **1 in 5 deaths** - over 443,000 - are smoking related[1]
- For every person who dies, 20 more suffer a **smoking-related illness** like cancer, heart disease, stroke, or lung disease[2]
- Smoking has been estimated to cost the United States **$96 billion in direct medical expenses** and **$97 billion in lost productivity** annually[1]

EVALUATING THE EVIDENCE

- The Task Force findings and recommendations for interventions that reduce or prevent tobacco use are based on systematic reviews of the available evidence.
- The systematic reviews look at the results of research and evaluation studies published in peer-reviewed journals and other sources.
- Each systematic review looks at the intervention's effectiveness and how it works in different populations and settings. If found effective, cost and return on investment are also reviewed when available.
- For each intervention, a summary of the systematic review, evidence gaps, and journal publications can be found on the Tobacco Use section of the website at www.thecommunityguide.org/tobacco. From this page, select the strategy you are interested in and click on the specific intervention you want to learn more about.

Community Preventive Services Task Force

The Guide to Community Preventive Services (The Community Guide) is an essential resource for people who want to know what works in public health. It provides evidence-based recommendations and findings about public health interventions and policies to improve health and promote safety. The Community Preventive Services Task Force (Task Force) - an independent, nonfederal, unpaid body of public health and prevention experts - bases its findings and recommendations on systematic reviews of the scientific literature. With oversight from the Task Force, scientists and subject matter experts from the Centers for Disease Control and Prevention conduct these reviews in collaboration with a wide range of government, academic, policy, and practice-based partners.

More information about how the Task Force conducts its reviews is available at www.thecommunityguide.org/about/methods.html.

SUMMARIZING THE FINDINGS ON TOBACCO

All Task Force findings and recommendations on tobacco use are available online at www.thecommunityguide.org/tobacco. Some of the Task Force recommendations related to tobacco use are below.

- ✓ **Reducing tobacco use initiation.** Raising the price of tobacco products can help prevent people from starting to use tobacco. For instance, adolescent tobacco use drops by a median of 3.7 percent for every 10 percent price hike. Additionally, mass-reach health communication interventions, primarily television broadcasts, have proven effective to reduce initiation among young people. Joint interventions such as mass-media campaigns combined with price increases and school- and community-based education have also proven effective in decreasing adolescent tobacco use by nearly 2.5 percent.
- ✓ **Increasing tobacco use cessation.** Strategies that can help more people quit using tobacco include raising produce prices and reducing financial barriers to treatment. Several recommended strategies work best in combination with others, such as mass media campaigns, mass-reach health communications interventions (primarily television broadcasts), mobile phone-based support programs, and systems that remind health care providers to counsel patients about quitting. For instance, combining mass-reach communication interventions that combine cessation messages with a quitline number and that are disseminated through multiple channels have been shown to increase call volume by a median of 132 percent.
- ✓ **Reducing exposure to environmental tobacco smoke (ETS).** Smoking policies such as bans and restrictions are particularly effective for curbing exposure to second-hand smoke. Studies show that smoking bans can reduce the level of ETS components (e.g. nicotine vapor) by a median of 72 percent within 12 months. Smoking bans, which entirely prohibit smoking in defined areas, reduce ETS exposure more than smoking restrictions, which limit smoking to designated areas.
- ✓ **Restricting minors' access to tobacco products.** Stronger laws for retailers who sell tobacco, active enforcement of these laws, and retailer education can help keep tobacco products out of young people's hands. These efforts can decrease tobacco sales to minors by a median of 33.5 percent and cut their tobacco use by a median of 5.8 percent.
- ✓ **Decreasing tobacco use among workers.** Strategies to boost quit rates in the workplace include policies restricting or banning smoking indoors and in public places, and incentive programs that reward workers for cutting back their tobacco use. Smoke-free policies can also save employers and workers money by reducing health care costs. For instance, quit rates can increase by a median of 6.4 percent among workers using these strategies. An employer could potentially save $10,246 per year for every smoker who quits due to a smoke-free workplace policy.

PUTTING THE FINDINGS TO WORK

As a public health decision maker, practitioner, community leader, or someone who can influence the health of your community, you can use The Community Guide to create a blueprint for success.

- ✓ Identify your community's needs. Review the intervention strategies recommended by the Task Force and determine which ones best match your needs. Develop evidence-based programs, services, and policies that make tobacco products less accessible, affordable, desirable, and accepted.
- ✓ Look for the National Cancer Institute's Cancer Control P.L.A.N.E.T. icon on The Community Guide website to find real-world programs related to the Task Force's recommendations that might be adaptable to your needs. Explore Cancer Control P.L.A.N.E.T.'s **Research-Tested Intervention Programs (RTIPs)**, which are community-based and clinical programs that have been evaluated, found to be effective, and published in a peer-reviewed journal. Learn more about RTIPs at www.thecommunityguide.org/cancer/screening/client-oriented/rtips.html.
- ✓ See how other communities have applied the Task Force recommendations for reducing tobacco use at www.thecommunityguide.org/CG-in-Action. Get ideas from their Community Guide in Action stories.
- ✓ Use **CDC's state and local resources** on smoking and tobacco at www.prevent.org/Topics/Community-Prevention.aspx to find best practice guides and other tools for implementing an effective tobacco control program.
- ✓ Consult **Partnership for Prevention Action Guide** at www.prevent.org/Topics/Tobacco-Control.aspx for suggestions on putting evidence-based recommendations on tobacco control into practice.



FOR MORE INFORMATION

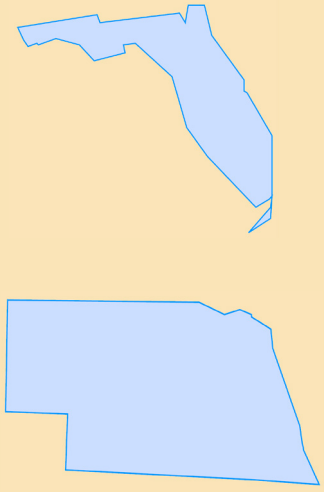
The Community Guide: Tobacco Use
www.thecommunityguide.org/tobacco

Office on Smoking and Health, CDC
www.cdc.gov/tobacco

CDC's Vital Signs: Adult Smoking in the U.S.
www.cdc.gov/vitalsigns/AdultSmoking

Preventing Tobacco Use Among Youth and Young Adults: We CAN Make the Next Generation Tobacco-Free
U.S. Surgeon General
www.surgeongeneral.gov/library/preventing-youth-tobacco-use

THE COMMUNITY GUIDE IN ACTION



Community-wide effort to make Florida tobacco free

Florida public health practitioners, community advocates, and residents joined forces to change state policy to stem the tide of death and disability caused by tobacco. Evidence-based interventions, including the ones in The Community Guide, were implemented across the state and led to substantial reductions in tobacco use and personal health care expenses.

Nebraska lays out a blueprint for success

Some communities are finding success by combining several recommended interventions. The City of Lincoln and Lancaster County, Nebraska used multiple strategies recommended in The Community Guide to build a phased approach to decrease local tobacco use. Beginning with community-wide education and engagement, their efforts led to substantial reductions in tobacco use in their county and eventually, to statewide policy changes, including a smoking ban modeled on the City of Lincoln's success.

Read more on these and other success stories in The Community Guide in Action series at www.thecommunityguide.org/CG-in-Action.

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www.thecommunityguide.org

The Guide to Community Preventive Services
THE COMMUNITY GUIDE
What Works to Promote Health

WHAT WORKS
Tobacco Use

Evidence-Based Interventions for Your Community

TASK FORCE FINDINGS ON TOBACCO USE

The Community Preventive Services Task Force (Task Force) has released the following findings on what works in public health to prevent tobacco use. These findings are compiled in The Guide to Community Preventive Services (The Community Guide) and listed in the table below. Use the findings to identify strategies and interventions you could use for your community.

Legend for Task Force Findings: ● Recommended ◆ Insufficient Evidence ▲ Recommended Against (See reverse for detailed descriptions.)

Intervention	Task Force Finding
Reducing Tobacco Use Initiation	
Increasing the unit price of tobacco products	●
Mass media campaigns when combined with other interventions	●
Smoke-free policies	●
Increasing Tobacco Use Cessation	
Increasing the unit price of tobacco products	●
Mass media campaigns when combined with other interventions	●
Mass-reach health communication interventions	●
Mobile phone-based interventions	●
Multicomponent interventions that include client telephone support	●
Smoke-free policies	●
Provider reminders when used alone	●
Provider reminders with provider education	●
Reducing client out-of-pocket costs for cessation therapies	●
Internet-based interventions	◆
Mass media – cessation contests	◆
Mass media – cessation series	◆
Provider assessment and feedback	◆
Provider education when used alone	◆

Intervention	Task Force Finding
Reducing Exposure to Environmental Tobacco Smoke	
Smoke-free policies	●
Community education to reduce exposure in the home	◆
Restricting Minors' Access to Tobacco Products	
Community mobilization with additional interventions	●
Sales laws directed at retailers when used alone	◆
Active enforcement of sales laws directed at retailers when used alone	◆
Community education about youth's access to tobacco products when used alone	◆
Retailer education with reinforcement and information on health consequences when used alone	◆
Retailer education without reinforcement when used alone	◆
Laws directed at minors' purchase, possession, or use of tobacco products when used alone	◆
Decreasing Tobacco Use Among Workers	
Smoke-free policies	●
Incentives and competitions to increase smoking cessation combined with additional interventions	●
Incentives and competitions to increase smoking cessation when used alone	◆

Visit the "Tobacco Use" page of The Community Guide website at www.thecommunityguide.org/tobacco to find summaries of Task Force findings and recommendations on tobacco use. Click on each topic area to find results from the systematic reviews, included studies, evidence gaps, and journal publications.

The Centers for Disease Control and Prevention provides administrative, research, and technical support for the Community Preventive Services Task Force.

UNDERSTANDING THE FINDINGS

The Task Force bases its findings and recommendations on systematic reviews of the scientific literature. With oversight from the Task Force, scientists and subject matter experts from the Centers for Disease Control and Prevention conduct these reviews in collaboration with a wide range of government, academic, policy, and practice-based partners. Based on the strength of the evidence, the Task Force assigns each intervention to one of the categories below.

CATEGORY	DESCRIPTION	ICON
Recommended	There is strong or sufficient evidence that the intervention is **effective**. This finding is based on the number of studies, how well the studies were designed and carried out, and the consistency and strength of the results.	
Insufficient Evidence	There is **not enough evidence** to determine whether the intervention is effective. This does not mean the intervention does not work. There is not enough research available or the results are too inconsistent to make a firm conclusion about the intervention's effectiveness. The Task Force encourages those who use interventions with insufficient evidence to evaluate their efforts.	
Recommended Against	There is strong or sufficient evidence that the strategy is **harmful or not effective**.	

Visit the "Systematic Review Methods" page on The Community Guide website at www.thecommunityguide.org/about/methods.html for more information about the methods used to conduct the systematic reviews and the criteria the Task Force uses to make findings and recommendations.

RESOURCES

You can use the following resources to guide the implementation of evidence-based strategies and put the Task Force findings to work.

- **Directory of Research Tested Intervention Programs (RTIPs)**
  National Cancer Institute and Substance Abuse and Mental Health Services
  http://rtips.cancer.gov/rtips

- **Success stories in reducing tobacco use**
  The Community Guide
  http://thecommunityguide.org/CG-in-Action/index.html

- **Best practices for tobacco control**
  Centers for Disease Control and Prevention
  www.cdc.gov/tobacco/stateandcommunity

- **Partnership for Prevention Action Guide**
  www.prevent.org/Topics/Tobacco-Control.aspx

- **State Tobacco Activities Tracking and Evaluation (STATE) System**
  Centers for Disease Control and Prevention
  http://apps.nccd.cdc.gov/statesystem

[Intervention Review]

Internet-based interventions for smoking cessation

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ABSTRACT

Background

The Internet is now an indispensable part of daily life for the majority of people in many parts of the world. It offers an additional means of effecting changes to behaviour such as smoking.

Objectives

To determine the effectiveness of Internet-based interventions for smoking cessation.

Search methods

We searched the Cochrane Tobacco Addiction Group Specialized Register. There were no restrictions placed on language of publication or publication date. The most recent search was conducted in April 2013.

Selection criteria

We included randomized and quasi-randomized trials. Participants were people who smoked, with no exclusions based on age, gender, ethnicity, language or health status. Any type of Internet intervention was eligible. The comparison condition could be a no-intervention control, a different Internet intervention, or a non-Internet intervention.

Data collection and analysis

Two authors independently assessed and extracted data. Methodological and study quality details were extracted using a standardized form. We extracted smoking cessation outcomes of six months follow-up or more, reporting short-term outcomes where longer-term outcomes were not available. We reported study effects as a risk ratio (RR) with a 95% confidence interval (CI). Clinical and statistical heterogeneity limited our ability to pool studies.

Main results

This updated review includes a total of 28 studies with over 45,000 participants. Some Internet programmes were intensive and included multiple outreach contacts with participants, whilst others relied on participants to initiate and maintain use.

Fifteen trials compared an Internet intervention to a non-Internet-based smoking cessation intervention or to a no-intervention control. Ten of these recruited adults, one recruited young adult university students and two recruited adolescents. Seven of the trials in adults

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Evidence-Based Strategies for Reducing Tobacco Use A Guide for CCOs

This guide is a resource to help CCOs think through their approach to reducing tobacco use. CCOs play an important role in helping their members quit, including: accurate assessment of member tobacco use status; benefit design (expanding coverage and reducing barriers); benefit promotion; implementing tobacco-free campus policies; and fostering partnerships with local public health agencies and other community stakeholders in order to create tobacco-free community environments.

CCOs have submitted comprehensive information about their cessation benefits to OHA via the 2014 cessation benefits survey; the results of the survey are reported in the Tobacco Cessation Services: 2014 Survey Report and can be accessed at *https://public.health.oregon.gov/PreventionWellness/TobaccoPrevention/Documents/tob_cessation_services_2014_survey_report.pdf*

The strategies are focused on CCO quality improvement activities and initiatives that will affect tobacco use among CCO members in 2015 and beyond. When reviewing the strategies CCOs are encouraged to work with internal and external partners as applicable including administrators, quality improvement staff, clinicians, hospitals, clinical advisory panels, community advisory councils and local health department administration and Tobacco Prevention and Education Program (TPEP) staff.

Things to consider include:

- ✓ Who needs to be included within your CCO or among contracted providers to develop and implement strategies to reduce tobacco use among your CCO members?
- ✓ What resources may be needed to support the tobacco reduction strategies outlined in this guide?
- ✓ What external partnerships could help support or lead your efforts to implement tobacco reduction strategies for your CCO?

Links to resources to support strategy implementation are provided where applicable. Tobacco Prevention and Education Program (TPEP) staff are available in every county and are ready to support CCO efforts to develop and implement policies and protocols to reduce tobacco use.

LOCAL CONTACTS:

Directory for Local Public Health Authorities: *http://public.health.oregon.gov/ProviderPartnerResources/LocalHealthDepartmentResources/Pages/lhd.aspx*

STATE CONTACT:

Oregon Public Health Division's Health Promotion and Chronic Disease Prevention Section, Scott Montegna, 971-673-0984, scott.p.montegna@state.or.us



Strategy: Identify Individuals Who Use Tobacco

Tobacco cessation interventions begin with identifying tobacco users. Health care delivery systems and providers should consistently identify and track tobacco use status and treat every tobacco user that seeks services in a health care setting. It is essential for CCOs to adopt systems for providers to identify tobacco users and use an evidence-based intervention each time a patient that uses tobacco is seen.

Plan-level steps to identify individuals who use tobacco include:	*We do this now*	*We are planning to do this*
• Reviewing medical and/or pharmacy claims data	☐	☐
• Intake assessments at office visits	☐	☐
• Health risk assessments	☐	☐
Encourage and incentivize your contracted providers to ask about and document tobacco use at every visit.		
• Educate all staff by offering trainings on tobacco dependence treatments and provide continuing education (CE) credits	☐	☐
• Provide resources to ensure ready access to cessation support services (Quit Line cards and information about effective tobacco use medications (e.g., establish a clinic fax-to-quit service, place medication information sheets in examination rooms).	☐	☐
• Provide feedback to clinicians about their performance. Evaluate the degree to which clinicians are identifying, documenting, and treating patients who use tobacco.	☐	☐

RESOURCES:

These resources provide guidance for providers asking about tobacco use status during intake assessments at office visits.

- ✓ **Treating Tobacco Dependence Practice Manual: Through a Systems-Change Approach -** This manual from the American Academy of Family Physicians takes a step-by-step approach in assessing tobacco cessation activities in your practice, implementing a system to ensure that tobacco use is systematically assessed and treated at every clinical encounter. *http://www.aafp.org/dam/AAFP/documents/patient_care/tobacco/practice-manual.pdf*
- ✓ **Treating Tobacco Use and Dependence: A Toolkit for Dental Office Teams -** This packet is designed to assist dental offices with integrating the brief intervention recommended by the guideline into standard office procedures and successfully intervene with their patients that use tobacco. It provides tools and resources to help you, help your patients, quit. *http://www.ctri.wisc.edu/HC.Providers/dentists/toolkit.pdf*
- ✓ **Treating Tobacco Use and Dependence: 2008 Update. Quick Reference Guide for Clinicians -** The guideline was designed to assist clinicians; smoking cessation specialists; and healthcare administrators, insurers, and purchasers in identifying and assessing tobacco users and in delivering effective tobacco dependence interventions. *http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/clinicians/references/quickref/tobaqrg.pdf*



Strategy: Offer Comprehensive Cessation Benefits and Reduce Access Barriers

The majority of tobacco users want to quit. CCOs, federally qualified health centers, behavioral health agencies, dental clinics and other health care systems have an important role in offering comprehensive, accessible cessation benefits to their employees and clients. Evidence shows that by providing both medication and counseling as a paid or covered benefit by a health insurance plan, there is an increase in the proportion of smokers who use cessation treatment, attempt to quit, and successfully quit.

Improve your plan's covered cessation benefits	*We do this now*	*We are planning to do this*
• Expand coverage to include all three forms of evidence-based counseling (individual, group, telephone) and all seven FDA approved medications (nicotine replacement therapy –gum, patch, lozenge, nasal spray, inhaler – and Bupropion SR and Varenicline).	☐	☐
• Remove lifetime or total cost limitations on benefits	☐	☐
Eliminate barriers for easier access		
• Remove requirements for prior authorization to access medications	☐	☐
• Remove requirements that members must participate in counseling to access medications	☐	☐

RESOURCES:

- ✓ **Helping Benefit Oregon Smokers: Health Plan Benefit Recommendations to Help Oregon Smokers Quit -** A resource that provides recommendations to guide health plans, employers, health care purchasers, health care providers, employees, and advocates as they embrace a standard of care and create a more effective cessation benefit. *http://smokefreeoregon.com/wp-content/uploads/2010/11/HBOS-brochure-web.pdf*
- ✓ **Checklist of recommended tobacco cessation benefits -** *http://www.smokefreeoregon.com/wp-content/uploads/2010/11/Health-Plans-HBOS-benefits.pdf*
- ✓ **Tobacco Cessation Service: 2014 Survey Report -** This report is the third time the Public Health Division has assessed the tobacco cessation benefits offered to members of Oregon's Medicaid program, the Oregon Health Plan. This report summarizes the services and benefits offered to Medicaid members as reported by each CCO. *https://public.health.oregon.gov/PreventionWellness/TobaccoPrevention/Documents/tob_cessation_services_2014_survey_report.pdf*



Strategy: Communicate and Promote Tobacco Cessation Benefit to All CCO Members

Evidence shows that it is essential to embed tobacco dependence strategies in the health care system to help tobacco users quit. Health care insurers should consistently promote the cessation benefits they offer and systematically refer tobacco users to the Quit Line to help tobacco users be successful in their quit attempts. Actively promoting these resources is a vital component to connecting tobacco users to evidence-based cessation resources, increasing quit attempts, and reducing smoking prevalence. Examples may include, providers' use of brief motivational interviewing with patients, establishing Quit Line e-referrals, mailings to identified tobacco users, and promotion of benefits in member handbook and newsletters.

Pro-actively reach out to all identified tobacco users to encourage them to quit or take advantage of their benefits.

	We do this now	*We are planning to do this*
• Providers' use of brief motivational interviewing with patients	☐	☐
• Establishing Quit Line e-referrals	☐	☐
• Mailings to identified tobacco users	☐	☐
• Promotion of benefits in member handbook and newsletters	☐	☐
• Promote quitting as a New Year's resolution, or connected to national campaigns, including World No Tobacco Day or the Great American Smokeout?	☐	☐

RESOURCES:

✓ **How to Design a Tobacco Cessation Insurance Benefit -** It is crucial that all health insurance plans and employers cover all of these treatments. But deciding to establish this coverage is only the first step. This document outlines the questions and issues plans and employers should consider after taking this critical first step, including communicating to plan members and providers about the benefit, and promoting the benefit to encourage tobacco users to quit. *http://www.lung.org/stop-smoking/tobacco-control-advocacy/reports-resources/tobacco-cessation-affordable-care-act/assets/how-to-design-a-tobacco.pdf*

Strategy: Support Effective Delivery of Cessation Benefits by Providers Through Quality Improvement Initiatives and Training

Clinicians must be adequately trained and prepared to treat tobacco dependence in their patients. Health care systems can ensure that clinicians and patients have the appropriate resources to address tobacco use and that a system is in place to provide feedback to clinicians on their tobacco dependence practices. CCOs can encourage or incentivize providers to use brief intervention strategies, such as the 5As or 2As & R. Clinic work-flows should be assessed to understand where best to use these strategies, and providers should have thorough knowledge of referral pathways to help tobacco users quit. Examples include staff trainings, provider manuals, provider newsletters, and provider website/handbook.

	We do this now	*We are planning to do this*
Ensure your provider network is aware of the existing benefits		
Information is shared by way of:		
• Staff trainings	☐	☐
• Provider manuals/handbook	☐	☐
• Provider newsletters	☐	☐
• Provider website	☐	☐
Provide tobacco-related trainings to contracted providers		
Training topics include:		
• Tobacco cessation benefits	☐	☐
• Systematic tobacco use assessment and documentation	☐	☐
• Referral strategies	☐	☐
• Motivational interviewing/behavioral counseling models (5A's or 2A's + R)	☐	☐
Systematically embed referral systems in clinic work-flows and electronic health records		
• Provider reminders incorporated into electronic health record	☐	☐
• Establish electronic referrals to Quit Line	☐	☐
• Establish referral system to community resources	☐	☐
• Implement closed-loop referrals	☐	☐
• Embedding decision support schematics or scripting in the EHR to help guide clinicians through an evidence-based intervention approach	☐	☐

RESOURCES:

- ✓ **Strengthening health systems for treating tobacco dependence in primary care. Part III: Training for primary care providers: brief tobacco interventions -** The purpose of this training guide is to improve primary care providers' knowledge, skills and confidence to routinely identify tobacco users and provide brief tobacco interventions to assist them in quitting. *http://apps.who.int/iris/bitstream/10665/84388/4/9789241505413_eng_Part-III_service_providers.pdf*
- ✓ **Five Major Steps to Intervention (The "5 A's") -** Successful intervention begins with identifying users and appropriate interventions based upon the patient's willingness to quit. The five major steps to intervention are the "5 A's": Ask, Advise, Assess, Assist, and Arrange. *http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/5steps.html*

Strategy: Tobacco-Free Campus Policy

There is no safe level of exposure to tobacco smoke. Tobacco smoke is toxic and contributes to deaths of smokers and non-smokers. Exposure to secondhand smoke can cause heart disease, cancer and worsen respiratory conditions such as asthma. Many of those that routinely seek health care services are especially vulnerable to the effects of secondhand smoke, including pregnant women, the elderly and people with chronic illness. In addition to the health risks associated with exposure to secondhand smoke, smoking and the use of other tobacco products in public places can normalize smoking behavior for youth. Establishing tobacco-free places creates a healthy environment and promotes social norms that support wellness. Several CCO administrative, contractor, and hospital campuses in Oregon have already gone tobacco-free to promote better health and a safer environment for patients, providers and other staff.

Adopt and Implement a Tobacco-Free Campus Policy

	We do this now	*We are planning to do this*
• Implement a tobacco-free campus policy for CCO administrative offices	☐	☐
• Require contracted providers to adopt tobacco-free campus policies	☐	☐
• Implement supportive practices, such as providing information about tobacco use and treatment, secondhand smoke, and local/ statewide cessation resources to patients, staff, and visitors	☐	☐

How can your CCO require contracted providers to adopt tobacco-free campus policies and encourage effective implementation practices, such as providing information about tobacco use and treatment, secondhand smoke, and local/ statewide cessation resources to patients, staff, and visitors?

RESOURCES:

- ✓ **Keeping Your Hospital Property Smoke-Free: Successful Strategies for Effective Policy Enforcement and Maintenance -** This how-to guide offers hospitals and other health care organizations useful strategies for implementing and enforcing a successful smoke-free or tobacco-free policy. *http://www.jointcommission.org/assets/1/18/Smoke_Free_Brochure2.pdf*
- ✓ **Implementing a Tobacco-Free Campus Initiative in Your Workplace -** This toolkit provides guidance for implementing a tobacco-free campus (TFC) initiative that includes a policy and comprehensive cessation services for employees. It is based on the Centers for Disease Control and Prevention's (CDC) experience with implementing the U.S. Department of Health and Human Services (HHS) Tobacco-Free HHS initiative. *http://www.cdc.gov/nccdphp/dnpao/hwi/toolkits/tobacco/index.htm*
- ✓ **Smoke-Free Hospital Toolkit: A Guide for Implementing Smoke-Free Policies -** Created by the University of Arkansas, a guide for implementing smoke-free hospital policies. Tobacco Free Nurses is the first national program created with the objectives of helping nurses quit, providing resources to nurses who want to help their patients quit and to promote tobacco control in the agenda of nursing organizations. *http://www.uams.edu/coph/reports/smokefree_toolkit/Hospital%20Toolkit%20Text.pdf*

Strategy: Work with Partners to Reduce Tobacco Prevalence in Communities Served By the CCO

CCOs/CACs can partner with local public health authorities to address tobacco prevention and cessation in the communities they serve. There are numerous evidence-based community interventions that are effective in reducing tobacco use and preventing youth initiation. These include: raising the price of tobacco through a tax, implementing tobacco retail environment interventions, tobacco-free work places and public spaces, and implementing cessation referral systems in social service agencies. By restricting access, promoting tobacco cessation and industry denormalization, we promote healthy, smokefree communities.

How can your CCO/Community Advisory Council (CAC) partner with your local public health authority (LPHA) to reduce tobacco prevalence in the communities you serve through cessation activities or policy change, including supporting the state and local implementation of comprehensive tobacco control programs? These programs are based on CDC best-practice recommendations, such as increasing the price of tobacco and increasing the number of tobacco-free environments.

RESOURCES:

- **Directory for Local Public Health Authorities -** Contact your local health department to connect with a local Tobacco Prevention and Education Program. *http://public.health.oregon.gov/ProviderPartnerResources/LocalHealthDepartmentResources/Pages/lhd.aspx*
- **OHA Public Health Tobacco Prevention and Education Program –** Learn about the statewide comprehensive program and policy approaches to reduce tobacco use. *http://public.health.oregon.gov/PreventionWellness/TobaccoPrevention/Pages/index.aspx*
- **CCO Community Advisory Councils -** CCOs are required to have community advisory councils who oversee the community health assessment and adopt the community health improvement plan. *http://www.oregon.gov/oha/OHPB/Pages/cac.aspx*
- **CDC The Community Guide Toolbox -** The Community Guide Toolbox is a collection of online public health materials that will help users assess and carry out evidence-based public health strategies and interventions to meet their community's critical health needs. *http://www.thecommunityguide.org/toolbox/index.html*

Strategy: Improve Outreach and Delivery of Cessation Benefits to Special Populations

The tobacco industry has invested billions of dollars in marketing tobacco to specific populations. Certain racial and ethnic groups, LBGTQ population, and those with serious and persistent mental illness have higher rates of tobacco use than the general population. The specific tobacco-related health risks for people in these groups must be considered in the design of tobacco control programs and strategies. Effective and culturally appropriate messaging and outreach to special populations can denormalize tobacco use and help existing tobacco users understand the resources to help them quit.

Communicate and outreach to members from special population groups, including those known to use tobacco at higher rates

	We do this now	*We are planning to do this*
• Special populations include:	☐	☐
• Native American	☐	☐
• African-American	☐	☐
• Latinos	☐	☐
• Asian and Pacific Islanders	☐	☐
• LGBTQ	☐	☐
• Non-English speaking	☐	☐
• Pregnant women	☐	☐
• Individuals with mental health conditions	☐	☐
• Youth	☐	☐

RESOURCES:

- ✓ **Tobacco Use and Pregnancy: Resources** - This website from the Centers for Disease Control and Prevention provide links to a variety of resources for smokers and their families and providers. *http://www.cdc.gov/reproductivehealth/TobaccoUsePregnancy/Resources.htm*
- ✓ **Smoking Cessation for Persons with Mental Illnesses: A Toolkit for Mental Health Providers** - This toolkit was developed for a broad continuum of mental health providers. The toolkit contains information and step-by-step instruction about low burden means of assessing readiness to quit, possible treatments, strategies for reducing relapse, and referral to community resources. *http://www.integration.samhsa.gov/Smoking_Cessation_for_Persons_with_MI.pdf*
- ✓ **National Native Network: Keep it Sacred -** The National Native Network website serves as a resource hub for culturally appropriate resources pertaining to tobacco cessation, tobacco products, chronic disease prevention, and the difference between commercial tobacco usage and sacred tobacco traditions among this population. *http://www.keepitsacred.org*
- ✓ **Regional Health Equity Coalitions -** Regional Equity Coalitions support local, culturally-specific activities designed by communities to reduce disparities and address the social determinants of health. *http://www.oregon.gov/oha/oei/Pages/rhec.aspx*

[Intervention Review]

Antidepressants for smoking cessation

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ABSTRACT

Background

There are at least three reasons to believe antidepressants might help in smoking cessation. Firstly, nicotine withdrawal may produce depressive symptoms or precipitate a major depressive episode and antidepressants may relieve these. Secondly, nicotine may have antidepressant effects that maintain smoking, and antidepressants may substitute for this effect. Finally, some antidepressants may have a specific effect on neural pathways (e.g. inhibiting monoamine oxidase) or receptors (e.g. blockade of nicotinic-cholinergic receptors) underlying nicotine addiction.

Objectives

The aim of this review is to assess the effect and safety of antidepressant medications to aid long-term smoking cessation. The medications include bupropion; doxepin; fluoxetine; imipramine; lazabemide; moclobemide; nortriptyline; paroxetine; S-Adenosyl-L-Methionine (SAMe); selegiline; sertraline; St. John's wort; tryptophan; venlafaxine; and zimeledine.

Search methods

We searched the Cochrane Tobacco Addiction Group Specialised Register which includes reports of trials indexed in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and PsycINFO, and other reviews and meeting abstracts, in July 2013.

Selection criteria

We considered randomized trials comparing antidepressant medications to placebo or an alternative pharmacotherapy for smoking cessation. We also included trials comparing different doses, using pharmacotherapy to prevent relapse or re-initiate smoking cessation or to help smokers reduce cigarette consumption. We excluded trials with less than six months follow-up.

Data collection and analysis

We extracted data and assessed risk of bias using standard methodological procedures expected by the Cochrane Collaboration.

The main outcome measure was abstinence from smoking after at least six months follow-up in patients smoking at baseline, expressed as a risk ratio (RR). We used the most rigorous definition of abstinence available in each trial, and biochemically validated rates if available. Where appropriate, we performed meta-analysis using a fixed-effect model.

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The problem

Tobacco imposes a considerable burden on society, including disease, lives lost, health care costs, and lost productivity. Smoking is the leading cause of premature death and preventable disease in Oregon and is responsible for about 7,000 deaths each year. Addressing tobacco use can save lives, improve health outcomes, and reduce health care and lost-productivity costs.

Multi-sector approach to addressing tobacco with evidence-based health practices

Conducing simultaneous multi-sector interventions maximizes the health and economic benefits of addressing tobacco use. Every dollar spent on coordinated, evidence-based tobacco control efforts can yield a savings of $55.[i] Coordinated efforts are effective across racial and ethnic groups, education levels, and levels of socioeconomic status.[ii]

All of the following recommendations for prioritization of tobacco prevention in health spending are informed by the *Community Guide*, unless otherwise noted. The Community Guide is the official collection of Community Preventive Services Task Force findings and the systematic reviews on which they are based. These recommendations translate this evidence for Oregon health systems within the state's current tobacco control and prevention environment.

1. **Provide leadership for development of smoke-free policies** in workplaces and public spaces. Like other employers, health systems can provide leadership for tobacco-related efforts in the communities they serve by establishing smoke-free campuses through workplace policies and contracts. They can also lend a persuasive voice to efforts to develop public-sector regulations that prohibit tobacco use in public areas.

   Evidence: *Smoke-free policies reduce tobacco use and exposure to second-hand smoke, and increase the number of tobacco users who quit. They also keep young people from initiating tobacco use and reduce acute cardiovascular events and other adverse tobacco-related health issues. Smoke-free policies can substantially reduce health care costs without adverse economic impact on businesses.*

2. **Educate policy makers about the positive effects of raising the per-unit price of tobacco products.** Raising the price of tobacco products increases the number of tobacco users who quit and reduces tobacco use, youth initiation, and negative health effects. The medical community is uniquely positioned to provide a persuasive perspective on what these population level effects mean for patients and their families.

   Evidence: *Health effects of raising the price of tobacco are proportional to the size of the price increase and the scale of implementation. Increasing the unit price for tobacco products by 20% has been shown to reduce consumption by 10.4%, prevalence of adult use by 3.6%, and youth initiation of tobacco use by young people by 8.6%. Raising tobacco prices substantially reduces healthcare costs, reduces tobacco-related disparities among income groups, and may reduce disparities by race and ethnicity.*

3. **Implement mass-reach communication interventions** to inform individual and public attitudes about tobacco use and secondhand smoke. Communication interventions should be coordinated with a statewide media strategy, and may include broadcast, print, and digital media and out-of-home placements (e.g., billboards, movie theaters, point of sale). Health system

communications that promote tobacco cessation may be evaluated for effectiveness by tracking quit line call volumes and tobacco use prevalence. Clear communication of cessation benefits to both tobacco users and healthcare providers increases use and impact of cessation interventions.

Evidence: *Strong evidence indicates that mass communication interventions decrease prevalence of tobacco use, increase cessation and use of cessation services, and prevent young people from initiating tobacco use. Mass-reach health communication interventions are cost-effective, with a benefit-to-cost ratio of 7:1 to 74:1. Savings from averted healthcare costs exceed intervention costs.*

4. ***Community engagement via local public health authorities*** to promote tobacco cessation, create tobacco-free community places, and identify and eliminate tobacco-related disparities. While Oregon's local health authorities are uniquely positioned to coordinate local and regional tobacco prevention initiatives, they receive only a fraction of the funding recommended by the Centers for Disease Control and Prevention. Support provided by health systems should be tailored to the needs of local communities.

   Evidence: *Coordinated statewide and local approaches to tobacco prevention and education are demonstrated to reduce initiation of tobacco use and secondhand smoke exposure, and to increase cessation.*[ii,]

Example of effectiveness of a multi-sector approach. From 2001 to 2010, the New York State Tobacco Control Program reported declines in the prevalence of smoking among adults and youth that outpaced declines nationally.[iii] As a result, smoking-attributable personal health care expenditures in New York in 2010 were $4.1 billion less than they would have been had the prevalence of smoking remained at 2001 levels.[iv]

DRAFT

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[Intervention Review]

Group behaviour therapy programmes for smoking cessation

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ABSTRACT

Background

Group therapy offers individuals the opportunity to learn behavioural techniques for smoking cessation, and to provide each other with mutual support.

Objectives

We aimed to determine the effects of smoking cessation programmes delivered in a group format compared to self-help materials, or to no intervention; to compare the effectiveness of group therapy and individual counselling; and to determine the effect of adding group therapy to advice from a health professional or to nicotine replacement. We also aimed to determine whether specific components increased the effectiveness of group therapy. We aimed to determine the rate at which offers of group therapy are taken up.

Search methods

We searched the Cochrane Tobacco Addiction Group Trials Register, with additional searches of MEDLINE and PsycINFO, including the terms behavior therapy, cognitive therapy, psychotherapy or group therapy, in July 2008.

Selection criteria

We considered randomized trials that compared group therapy with self help, individual counselling, another intervention or no intervention (including usual care or a waiting list control). We also considered trials that compared more than one group programme. We included those trials with a minimum of two group meetings, and follow up of smoking status at least six months after the start of the programme. We excluded trials in which group therapy was provided to both active therapy and placebo arms of trials of pharmacotherapies, unless they had a factorial design.

Data collection and analysis

We extracted data in duplicate on the participants, the interventions provided to the groups and the controls, including programme length, intensity and main components, the outcome measures, method of randomization, and completeness of follow up.

The main outcome measure was abstinence from smoking after at least six months follow up in patients smoking at baseline. We used the most rigorous definition of abstinence in each trial, and biochemically validated rates where available. Subjects lost to follow up were analysed as continuing smokers. Effects were expressed as a relative risk for cessation. Where possible, we performed meta-analysis using a fixed-effect (Mantel-Haenszel) model.

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Annals of Internal Medicine

CLINICAL GUIDELINE

Behavioral and Pharmacotherapy Interventions for Tobacco Smoking Cessation in Adults, Including Pregnant Women: U.S. Preventive Services Task Force Recommendation Statement

Albert L. Siu, MD, MSPH, for the U.S. Preventive Services Task Force*

Description: Update of the 2009 U.S. Preventive Services Task Force (USPSTF) recommendation on counseling and interventions to prevent tobacco use and tobacco-related disease in adults, including pregnant women.

Methods: The USPSTF reviewed the evidence on interventions for tobacco smoking cessation that are relevant to primary care (behavioral interventions, pharmacotherapy, and complementary or alternative therapy) in adults, including pregnant women.

Population: This recommendation applies to adults aged 18 years or older, including pregnant women.

Recommendations: The USPSTF recommends that clinicians ask all adults about tobacco use, advise them to stop using tobacco, and provide behavioral interventions and U.S. Food and Drug Administration–approved pharmacotherapy for cessation to adults who use tobacco. (A recommendation)

The USPSTF recommends that clinicians ask all pregnant women about tobacco use, advise them to stop using tobacco, and provide behavioral interventions for cessation to pregnant women who use tobacco. (A recommendation)

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of pharmacotherapy interventions for tobacco cessation in pregnant women. (I statement)

The USPSTF concludes that the current evidence is insufficient to recommend electronic nicotine delivery systems for tobacco cessation in adults, including pregnant women. The USPSTF recommends that clinicians direct patients who smoke tobacco to other cessation interventions with established effectiveness and safety (previously stated). (I statement)

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For author affiliation, see end of text.

* For a list of the members of the USPSTF, see the Appendix (available at www.annals.org).

This article was published online first at www.annals.org on 22 September 2015.

The U.S. Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care services for patients without related signs or symptoms.

It bases its recommendations on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision making to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.

Summary of Recommendations and Evidence

The USPSTF recommends that clinicians ask all adults about tobacco use, advise them to stop using tobacco, and provide behavioral interventions and pharmacotherapy U.S. Food and Drug Administration (FDA)–approved pharmacotherapy for cessation to adults who use tobacco. (A recommendation)

The USPSTF recommends that clinicians ask all pregnant women about tobacco use, advise them to stop using tobacco, and provide behavioral interventions for cessation to pregnant women who use tobacco. (A recommendation)

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of pharmacotherapy interventions for tobacco cessation in pregnant women. (I statement)

The USPSTF concludes that the current evidence is insufficient to recommend electronic nicotine delivery systems (ENDS) for tobacco cessation in adults, including pregnant women. The USPSTF recommends that clinicians direct patients who smoke tobacco to other cessation interventions with established effectiveness and safety (previously stated). (I statement)

See the Clinical Considerations section for suggestions for practice regarding the I statements.

See the **Figure** for a summary of the recommendations and suggestions for clinical practice.

See also:

Related article 1
Summary for Patients 2

U.S. Preventive Services TASK FORCE
www.USPreventiveServicesTaskForce.org

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Figure. Behavioral and pharmacotherapy interventions for tobacco cessation in adults, including pregnant women: clinical summary.

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U.S. Preventive Services TASK FORCE
www.USPreventiveServicesTaskForce.org

Behavioral and Pharmacotherapy Interventions for Tobacco Smoking Cessation in Adults, Including Pregnant Women: Clinical Summary

Population	Nonpregnant adults aged ≥18 y	Pregnant adults aged ≥18 y	Pregnant adults aged ≥18 y	All adults aged ≥18 y
Recommendation	Provide pharmacotherapy and behavioral interventions for cessation. Grade: A	Provide behavioral interventions for cessation. Grade: A	Pharmacotherapy interventions: No recommendation. Grade: I statement	ENDS: No recommendation. Grade: I statement
Assessment	The 5 A's framework is a useful strategy for engaging patients in smoking cessation discussions. The 5 A's include asking every patient about tobacco use, advising all tobacco users to quit, assessing the willingness of all tobacco users to make an attempt to quit assisting tobacco users with their attempt to quit, and arranging follow-up.			
Behavioral Counseling Interventions	Behavioral interventions alone (in-person behavioral support and counseling, telephone counseling, and self-help materials) or combined with pharmacotherapy substantially improve achievement of tobacco cessation.	Behavioral interventions substantially improve achievement of tobacco smoking abstinence, improve infant birthweight, and reduce risk for preterm birth.		
Pharmacotherapy Interventions	Pharmacotherapy interventions, including NRT, bupropion SR, and varenicline–with or without behavioral counseling interventions–substantially improve achievement of tobacco cessation.		There is inadequate or no evidence on the benefits of NRT, bupropion SR, or varenicline to achieve tobacco cessation or improve perinatal outcomes in infants.	There is inadequate evidence on the benefit of ENDS to achieve tobacco cessation or improve perinatal outcomes in infants.
Balance of Benefits and Harms	The USPSTF concludes with high certainty that the net benefit of behavioral interventions and FDA-approved pharmacotherapy for tobacco cessation, alone or in combination, is substantial.	The USPSTF concludes with high certainty that the net benefit of behavioral interventions for tobacco cessation on perinatal outcomes and smoking abstinence is substantial.	The USPSTF concludes that the evidence on pharmacotherapy interventions for tobacco cessation is insufficient because of a lack of studies, and the balance of benefits and harms cannot be determined.	The USPSTF concludes that the evidence on the use of ENDS for tobacco cessation is insufficient, and the balance of benefits and harms cannot be determined.
Other Relevant USPSTF Recommendations	The USPSTF recommends that primary care clinicians provide interventions, including education or brief counseling, to prevent the initiation of tobacco use in school-aged children and adolescents. This recommendation is available on the USPSTF Web site (www.uspreventiveservicestaskforce.org).			

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to www.uspreventiveservicestaskforce.org.

ENDS = electronic nicotine delivery system; FDA = U.S. Food and Drug Administration; The 5 A's = Five Major Steps to Intervention; NRT = nicotine replacement therapy; USPSTF = U.S. Preventive Services Task Force.

Appendix Table 1 describes the USPSTF grades, and Appendix Table 2 describes the USPSTF classification of levels of certainty about net benefit (both tables are available at www.annals.org).

RATIONALE

Importance

Tobacco use is the leading preventable cause of disease, disability, and death in the United States. Cigarette smoking results in more than 480 000 premature deaths each year and accounts for approximately 1 in every 5 deaths (1). In pregnant women, smoking increases the risk for congenital anomalies; perinatal complications, such as preterm birth, fetal growth restriction, and placental abruption; miscarriage and stillbirth; and neonatal or pediatric complications, such as sudden infant death syndrome and impaired lung function in childhood (1–4). An estimated 42.1 million U.S. adults (nearly 18% of the population) currently smoke (5).

Recognition of Behavior

The benefits of assessing patients' smoking behavior are well-established. Common approaches for clinicians include recording a patient's smoking status as a vital sign or using The 5 A's: 1) Ask about smoking; 2) Advise to quit through clear, personalized messages; 3) Assess willingness to quit; 4) Assist in quitting; and 5) Arrange follow-up and support). Another approach is

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"Ask, Advise, Refer," which encourages clinicians to ask patients about tobacco use, advise them to quit, and refer them to telephone quit lines and/or other evidence-based cessation interventions.

Benefits of Interventions

Nonpregnant Adults

The USPSTF found convincing evidence that behavioral interventions (including in-person behavioral support and counseling, telephone counseling, and self-help materials) alone or combined with pharmacotherapy substantially improve achievement of tobacco cessation in nonpregnant adults who smoke. The USPSTF found convincing evidence that pharmacotherapy interventions, including nicotine replacement therapy (NRT), bupropion hydrochloride sustained-release (buproprion SR), and varenicline–with or without behavioral counseling interventions–substantially improve achievement of tobacco cessation in nonpregnant adults who smoke. The USPSTF also found convincing evidence that using 2 types of NRT moderately improves achievement of tobacco smoking cessation over using 1 type and that addition of NRT to treatment with bupropion SR provides additional benefit over use of bupropion SR alone. The USPSTF found inadequate evidence to determine the effect of ENDS on achievement of tobacco smoking cessation.

Pregnant Women

The USPSTF found convincing evidence that behavioral interventions substantially improve achievement of tobacco smoking abstinence in pregnant women, increase infant birthweight, and reduce risk for preterm birth. The USPSTF found inadequate evidence on the benefits of NRT and no evidence on the benefits of bupropion SR, varenicline, or ENDS to achieve tobacco cessation in pregnant women who smoke or to improve perinatal outcomes in infants.

Harms of Interventions

Nonpregnant Adults

The USPSTF determined that there is adequate evidence to bound the magnitude of harms of behavioral interventions for tobacco cessation in nonpregnant adults who smoke as small to none. The USPSTF found adequate evidence that the harms of NRT, bupropion SR, or varenicline for tobacco cessation in adults who smoke are small. The USPSTF found inadequate evidence to determine the harms of ENDS.

Pregnant Women

The USPSTF determined that there is adequate evidence to bound the magnitude of harms of behavioral interventions for tobacco cessation in pregnant women who smoke as small to none. The USPSTF found inadequate evidence on the harms of NRT and no evidence on the harms of bupropion SR, varenicline, or ENDS for tobacco cessation in pregnant women who smoke.

USPSTF Assessment

The USPSTF concludes with high certainty that the net benefit of behavioral interventions and FDA-approved pharmacotherapy for tobacco cessation, alone or combined, in nonpregnant adults who smoke is substantial.

The USPSTF concludes with high certainty that the net benefit of behavioral interventions for tobacco cessation on perinatal outcomes and smoking abstinence in pregnant women who smoke is substantial.

The USPSTF concludes that the evidence on pharmacotherapy interventions for tobacco cessation in pregnant women is insufficient because of a lack of studies, and the balance of benefits and harms cannot be determined.

The USPSTF concludes that the evidence on the use of ENDS for tobacco smoking cessation in adults, including pregnant women, is insufficient, and the balance of benefits and harms cannot be determined. The USPSTF has identified the lack of well-designed, randomized, controlled trials (RCTs) on ENDS that report smoking abstinence or adverse events as a critical gap in the evidence.

CLINICAL CONSIDERATIONS

Patient Population Under Consideration

This recommendation applies to adults aged 18 years or older, including pregnant women. The USPSTF previously issued a separate recommendation statement on primary care interventions for tobacco use in children and adolescents (available at www.uspreventiveservicestaskforce.org). Although the USPSTF acknowledges that tobacco may be used in other forms and that other substances aside from tobacco may be smoked, they are not the focus of this recommendation.

Assessment of Risk

According to the 2012–2013 National Adult Tobacco Survey, smoking prevalence is higher in the following groups: men; adults aged 25 to 44 years; persons with a race or ethnicity category of "other, non-Hispanic"; persons with a GED (vs. graduate-level education); persons with an annual household income of less than $20 000; and persons who are lesbian, gay, bisexual, or transgender (6). Higher rates of smoking have been found in persons with mental health conditions (7).

Implementation Considerations of Behavioral and Pharmacotherapy Interventions

The information that follows on the implementation of interventions for smoking cessation draws from the USPSTF systematic evidence review (8) and the 2008 Public Health Service guidelines (9).

Assessment of Smoking Status

The 5 A's framework (available at www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/5steps.html) is a useful strategy

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Table. Components of Effective Behavioral Interventions for Tobacco Cessation

Intensity
- Both minimal (<20 min in 1 visit) and intensive (≥20 min plus >1 follow-up visit) physician-advice interventions effectively increase the proportion of adults who successfully quit smoking and remain abstinent for ≥6 mo.
- There is a dose–response relationship between the intensity of counseling and cessation rates (i.e., more or longer sessions improve cessation rates).

Duration
- Brief, in-person behavioral counseling sessions (<10 min) effectively increase the proportion of adults who successfully quit smoking and remain abstinent for 1 y.
- Although less effective than longer interventions, even minimal interventions (<3 min) have been found to increase cessation rates in some studies.

Frequency
- Multiple sessions should be provided; according to the Public Health Service guidelines, patients should receive ≥4 in-person counseling sessions.
- Cessation rates may plateau after 90 min of total counseling contact time.

Format
- In-person behavioral counseling sessions (individual or group counseling)
- Telephone counseling
- Tailored, print-based self-help materials

Provider
- In-person behavioral counseling sessions: various types of primary care providers, including physicians, nurses, psychologists, social workers, and cessation counselors
- Telephone counseling: professional counselors or health care providers who are trained to offer advice over the telephone

Content
- Assessment of smoking status
  - Ask every patient about tobacco use
  - Advise all tobacco users to quit
  - Assess willingness of all tobacco users to make an attempt to quit
  - Assist all tobacco users with their attempt to quit
  - Arrange follow-up
- Effective counseling interventions provide social support and training in practical problem-solving skills
  - Training in problem-solving skills includes helping persons who smoke to recognize situations that increase their risk for smoking, develop coping skills to overcome common barriers to quitting, and develop a plan to quit
  - Basic information about smoking and successful quitting should also be provided
  - Complementary practices that improve cessation rates include motivational interviewing, assessing readiness to change, and offering more intensive counseling or referrals

for engaging patients in discussions about smoking cessation. This program includes the following: 1) Asking every patient about tobacco use, 2) Advising all tobacco users to quit, 3) Assessing their willingness to attempt to quit, 4) Assisting with attempts to quit, and 5) Arranging follow-up (10). "Ask, Advise, Refer" is another approach and involves asking patients about tobacco use, advising those who smoke to quit, and referring them to evidence-based interventions. Treating smoking status as a vital sign and recording smoking status at every health visit are also frequently used to assess smoking status. Because many pregnant women who smoke do not report it, using multiple-choice questions to assess smoking status in this group may improve disclosure (9).

Nonpregnant Adults

Both intervention types (pharmacotherapy and behavioral interventions) are effective and recommended; combinations of interventions are most effective, and all should be offered. The best and most effective combinations are those that are acceptable to and feasible for an individual patient; clinicians should consider the patient's specific medical history and preferences and offer and provide the combination that works best for the patient.

Behavioral Interventions. Many behavioral interventions are available to encourage smoking cessation in adults. These interventions can be delivered in the primary care setting or can be referred to community settings with feedback to the primary care provider. Effective behavioral interventions include in-person behavioral support and counseling, telephone counseling, and self-help materials (**Table**). Behavioral interventions may increase rates of smoking abstinence from a baseline range of approximately 5% to 11% in control groups to 7% to 13% in intervention groups (8).

Both minimal (<20 minutes in 1 visit) and intensive (≥20 minutes plus >1 follow-up visit) physician-advice interventions effectively increase the proportion of adults who successfully quit smoking and remain abstinent for at least 6 months (8).

Brief, in-person behavioral counseling sessions (<10 minutes) effectively increase the proportion of adults who successfully quit smoking and remain abstinent for 1 year. Although less effective than longer interventions, even minimal interventions (<3 minutes) have increased cessation rates in some studies (9).

There is a dose–response relationship between the intensity of counseling and cessation rates (that is, more or longer sessions improve cessation rates) (9).

Several sessions should be provided; according to the Public Health Service guidelines, patients should receive at least 4 in-person counseling sessions (9).

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Cessation rates may plateau after 90 minutes of total counseling contact time (9).

Effective interventions can be delivered by various types of primary care providers, including physicians, nurses, psychologists, social workers, and cessation counselors (8, 9).

Both individual and group counseling are effective (9).

Effective counseling interventions provide social support and training in practical problem-solving skills (9).

Training in problem-solving skills includes helping persons who smoke to recognize situations that increase their risk for smoking, develop coping skills to overcome common barriers to quitting, and develop a plan to quit.

Basic information about smoking and successful quitting should be provided.

Complementary practices that improve cessation rates include motivational interviewing, assessing readiness to change, and offering more intensive counseling or referrals (9).

Telephone counseling interventions are effective (8, 9).

Effective interventions provide at least 3 telephone calls (8).

Telephone counseling can be provided by professional counselors or health care providers who are trained to offer advice over the telephone.

Providing self-help materials (primarily print-based) that are tailored to the individual patient (that is, beyond a brochure that simply describes the health effects of smoking) is also effective in improving smoking abstinence (8). Evidence on nontailored, print-based, self-help materials; computer-based programs; and mobile phone–based interventions (such as a mHEALTH) is mixed, although several trials show promise (8).

Pharmacotherapy. The only pharmacotherapy interventions approved by the FDA for the treatment of tobacco dependence in adults are bupropion SR, varenicline, and NRT (including nicotine transdermal patches, lozenges, gum, inhalers, or nasal spray).

Evidence suggests that rates of smoking abstinence may increase from approximately 10% in control groups (placebo or no pharmacotherapy) to 17% in persons using any form of NRT, from roughly 11% in control groups (placebo or no bupropion SR) to 19% in those using bupropion SR, and from approximately 12% in control groups (placebo) to 28% in those using varenicline (8).

Information on dosing regimens is available in the package inserts of individual medications or at http://betobaccofree.hhs.gov. Information for consumers on FDA-approved pharmacotherapy for smoking cessation is available at www.fda.gov/ForConsumers/ConsumerUpdates/ucm198176.htm.

Combinations of Pharmacotherapy. Using 2 types of NRT has been found to be more effective than using a single type. In particular, there was evidence that combining a nicotine patch with a rapid-delivery form of NRT is more effective than using a single type.

Some studies suggest that NRT in combination with bupropion SR may be more efficacious than bupropion SR alone but not necessarily NRT alone (8).

Combinations of Behavioral and Pharmacotherapy Interventions. Combining behavioral and pharmacotherapy interventions may increase cessation rates from approximately 8% to 14% (11) compared with usual care or minimal behavioral interventions (such as self-help materials or brief advice on quitting).

These combination interventions often have behavioral components delivered by specialized cessation counselors or trained staff and often use NRT.

Combination interventions often involve several sessions (≥4) and tend to be more successful with more sessions.

The largest effect was found in interventions that provided 8 or more sessions, although the difference in effect among the number of sessions was not significant.

Contact time ranged from 0 to greater than 300 minutes; interventions lasting 91 to 300 minutes were most common.

The addition of behavioral support to pharmacotherapy also significantly increased cessation rates from approximately 18% in persons using pharmacotherapy alone to 21% in those using a combination of pharmacotherapy and behavioral support.

Intensity of behavioral support ranged from 0 to greater than 300 minutes of contact; interventions most often involved greater than 91 minutes of contact (roughly 40% were 91 to 300 minutes, and 60% were >300 minutes).

Pregnant Women

Behavioral Interventions. Effective behavioral interventions in pregnant women who smoke include counseling, feedback, health education, incentives, and social support. Compared with usual care or controls, behavioral interventions can increase rates of smoking abstinence from approximately 11% to 15% in pregnant women.

Effective behavioral interventions provided more intensive counseling than minimal advice and other standard components of usual care (9).

Counseling sessions augmented with messages and self-help materials tailored for pregnant women who smoke increased abstinence rates during pregnancy compared with brief, generic counseling interventions alone (9).

Counseling specific to pregnant women should include messages about the effects of smoking on both maternal and fetal health and clear, strong advice to quit as soon as possible. Although smoking cessation at any point during pregnancy yields substantial health benefits for the expectant mother and baby, quitting early in pregnancy provides the greatest benefit to the fetus (9).

Other Interventions

Health care system–based strategies that have been shown to improve rates of clinical interventions for smoking cessation in primary care settings include

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implementing an identification system for tobacco users; providing education, resources, and feedback to promote clinician intervention; and dedicating staff to provide treatment for tobacco dependence and assessing the delivery of this treatment in staff performance evaluations (9).

Useful Resources

Primary care clinicians may find the following resources useful in talking with adults and pregnant women about smoking cessation: Centers for Disease Control and Prevention fact sheets on quitting smoking (www.cdc.gov/tobacco/data_statistics/fact_sheets/cessation/quitting/index.htm), the U.S. Department of Health and Human Services' BeTobaccoFree (http://betobaccofree.hhs.gov/quit-now/index.html#professionals), the U.S. Department of Health and Human Services' SmokeFreeWomen (http://women.smokefree.gov/pregnancy-motherhood.aspx), and the Public Health Service's 2008 clinical practice guidelines (9).

In addition, the following resources may be useful to primary care clinicians and practices trying to implement interventions for smoking cessation: the Substance Abuse and Mental Health Services Administration–Health Resources and Services Administration Center for Integrated Health Solutions' resources for smoking cessation (www.integration.samhsa.gov/health-wellness/wellness-strategies/tobacco-cessation-2), Centers for Disease Control and Prevention state and community resources for tobacco-control programs (www.cdc.gov/tobacco/stateandcommunity/index.htm), and the World Health Organization's toolkit for delivering brief smoking interventions in primary care (www.who.int/tobacco/publications/smoking_cessation/9789241506953/en).

Suggestions for Practice Regarding the I Statements

Pharmacotherapy for Pregnant Women

Although smoking prevalence is lower in pregnant women than nonpregnant women of the same age, approximately 1 in 6 pregnant women aged 15 to 44 years smoke (7). Smoking during pregnancy slows fetal growth, doubles the risk for delivering a baby with low birthweight, and increases the risk for fetal death by 25% to 50%. For women in whom behavioral counseling does not work, other options to promote smoking cessation may be beneficial.

A few studies have evaluated the benefit of NRT on perinatal and child health outcomes. Although results generally suggest a potential benefit, the overall evidence is too limited to draw clear conclusions. Nicotine replacement therapy is a pregnancy category D medication, which means that there is positive evidence of fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans. However, it has been suggested that NRT may be safer than smoking during pregnancy (4, 12). Potential adverse events reported include increased rates of cesarean delivery, slightly increased diastolic blood pressure, and skin reactions to the patch. Potential adverse events reported in nonpregnant adults include higher rates of low-risk cardiovascular events, such as tachycardia. There is no evidence of perinatal harms from NRT, although few trials reported consistently on these adverse events.

The USPSTF identified no studies on bupropion SR or varenicline pharmacotherapy during pregnancy. These drugs are both pregnancy category C, which means that animal reproduction studies have shown an adverse effect on the fetus but there are no adequate well-controlled studies in humans.

In the absence of clear evidence on the balance of benefits and harms of pharmacotherapy in pregnant women, clinicians are encouraged to consider the severity of smoking behavior in each patient and engage in shared decision making to determine the best individual treatment course.

ENDS

Approximately 69% of adults who smoke daily report interest in quitting, and roughly 43% attempted to quit in the previous year (1). To date, no ENDS manufacturer has applied for or received FDA approval to market their product for smoking cessation purposes. According to a small 2013 study, approximately two thirds of physicians reported that they believed that electronic cigarettes (e-cigarettes) were a helpful aid for smoking cessation, and 35% recommended them to patients (13). A recent small survey of e-cigarette users found that 56% reported using them to quit or reduce cigarette use, and 26% reported using them to smoke in places where conventional cigarettes were banned (14). Because of the perception by the public and clinicians that ENDS may be used for quitting conventional smoking, the USPSTF reviewed the evidence in this area. No studies evaluated the use of ENDS for smoking cessation in pregnant women or adolescents. The USPSTF identified only 2 RCTs that evaluated the effect of e-cigarettes on smoking abstinence in adults and found mixed results. Neither study reported any serious adverse events related to ENDS use; however, potential concerns raised in other literature include the unknown safety and toxicity of their components and aerosols (11, 15), and poisoning in children who mishandle nicotine cartridges (16). How the ingredients in ENDS may affect a fetus is also unknown. Overall, the USPSTF found the evidence on the use of ENDS as a smoking cessation tool in adults, including pregnant women, and adolescents to be insufficient.

Additional Approaches to Prevention

Given the public health significance of the consequences of tobacco use, numerous public health interventions aim to prevent tobacco use and promote smoking cessation. The Community Preventive Services Task Force offers several recommendations on interventions that can be used in community settings (available at www.thecommunityguide.org/tobacco/index.html). The Surgeon General's report, "The Health Consequences of Smoking–50 Years of Progress," discusses initiatives to end the tobacco use epidemic in the United States (1). In addition, the USPSTF recom-

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mends that primary care clinicians provide interventions, including education or brief counseling, to prevent the initiation of tobacco use among school-aged children and adolescents (available at www.uspreventiveservicestaskforce.org).

OTHER CONSIDERATIONS

Research Needs and Gaps

A large body of evidence on interventions for smoking cessation already exists, and the overall benefit of pharmacotherapy and behavioral counseling to promote smoking cessation is well-established. However, further research is still needed to elucidate specific effective features of complex behavioral counseling interventions, benefits of pharmacotherapy in specific subpopulations, and the efficacy of newer technology-based interventions. Although numerous behavioral interventions for smoking cessation are available to primary care clinicians, further research is needed to better clarify the effects of varying levels of intensity (such as how the number of sessions and number of minutes per session affect continuous abstinence rates), which settings of behavioral counseling interventions are most conducive to quitting (individual vs. group, health vs. community, and primary care vs. specialty), and ways to tailor self-help materials. Further research is needed on the benefits and harms of pharmacotherapy in specific subpopulations, such as pregnant women and adults with mental health conditions. Research that directly compares types of pharmacotherapy in different populations may help inform providers on which interventions to use with which patients. Additional research is also needed on interventions for light or nondaily smokers and to better understand the effectiveness of newer technology platforms for interventions for smoking cessation, such as Internet-based programs, mobile or smartphone applications, and text-messaging programs. Although no ENDS manufacturer has applied to the FDA to have their product approved as a therapeutic device, because of the perception by both the public and clinicians that ENDS may be used as an option for quitting conventional smoking, further research is needed on the safety, benefits, and harms of ENDS.

DISCUSSION

Burden of Disease

Tobacco use is the leading preventable cause of disease, disability, and death in the United States. Smoking increases the risk for all-cause mortality and has been found to increase risk for various types of cancer (such as lung, liver, and colorectal), respiratory diseases (such as chronic obstructive pulmonary disease and tuberculosis), cardiovascular disease (such as stroke from secondhand smoke), diabetes, impaired immune function and autoimmune disease (such as rheumatoid arthritis), eye disease (such as age-related macular degeneration), and erectile dysfunction in men. Smoking early in pregnancy has been found to cause ectopic pregnancy and orofacial clefts in infants (1).

According to National Health Interview Survey data from 2013, a total of 42.1 million adults in the United States (17.8%) smokes cigarettes (5). Rates are higher among men; adults aged 24 to 44 years; lesbian, gay, bisexual, or transgender adults; multiracial groups and American Indians or Alaska Natives; persons whose highest education level attained is a GED; and persons living below the poverty level (5). Adults with mental health conditions have higher smoking rates and tend to smoke a higher average number of cigarettes than adults without mental health conditions. Approximately 27% of persons with a mental health or substance use disorder smoke (17).

Based on data from the Pregnancy Risk Assessment and Monitoring System, 23.2% of women smoked during the 3 months before conception (18). Data from 2011 showed that 55% of women quit smoking during pregnancy, roughly 10% of pregnant women smoked during the last 3 months of pregnancy, and 40% of women relapsed within 6 months of delivery (19). Smoking during pregnancy is associated with fetal growth restriction, preterm delivery, and sudden infant death syndrome. Prenatal smoking contributed to an estimated 5.3% to 7.7% of preterm deliveries, 13.1% to 19.0% of low-birthweight term deliveries, 23.2% to 33.6% of cases of sudden infant death syndrome, and 5.0% to 7.3% of preterm-related deaths in 2002 (1).

Quitting smoking is one of the most important and yet challenging preventive health measures a person can take to improve his or her health. Most smokers make several serious attempts to quit before achieving permanent abstinence.

Scope of Review

The current review focused on appraising evidence on interventions for smoking cessation that are relevant to primary care (behavioral interventions, pharmacotherapy, and complementary or alternative therapy) in adults, including pregnant women. Only pharmacotherapy interventions that were approved by the FDA as first-line agents for smoking cessation were included (NRT, bupropion SR, and varenicline). Health outcomes included all-cause mortality, tobacco-related mortality and morbidity, and perinatal mortality and morbidity. Smoking-cessation outcomes had to be reported at 6 months or later to be included; findings on smoking reduction (based on frequency or quantity only), intention to quit, and cessation at less than 6 months were excluded. The USPSTF also evaluated adverse events reported at any time point.

Effectiveness of Interventions

Nonpregnant Adults

Behavioral Interventions. The USPSTF reviewed 11 good- or fair-quality systematic reviews on behavioral interventions, including complementary or alternative therapies, and smoking-cessation outcomes (8). Evidence on increasing smoking abstinence was strongest for physician and nurse advice, tailored self-help materials, and telephone counseling. Based on a 2013 sys-

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tematic review of 28 studies (*n* = 22 239) (20), rates of smoking abstinence at 6 months or more were 8.0% in groups that received physician advice compared with 4.8% in groups that received no advice or usual care (risk ratio [RR], 1.76 [95% CI, 1.56 to 1.96]). Based on pooled analyses of 35 studies from a 2013 systematic review that evaluated advice delivered by nurses, 13.3% of participants who received interventions from nurses achieved smoking abstinence at 6 months or more compared with 11.3% of those who received usual care or minimal intervention (RR, 1.29 [CI, 1.20 to 1.39]) (21). When stratified by intensity level, both minimal advice (defined as a single session lasting <20 minutes with ≤1 follow-up session) and intensive advice (defined as a single session lasting ≥20 minutes or >1 follow-up session) from a physician significantly increased cessation rates compared with no advice. In a subset of 15 trials that directly compared intensive versus minimal advice from physicians, intensive advice significantly increased smoking abstinence compared with minimal advice (RR, 1.37 [CI, 1.20 to 1.56]) (20). Based on pooled analyses of 32 studies from a 2014 review of print-based self-help materials (*n* = 40 890), participants who received tailored self-help materials showed a significantly higher rate of smoking abstinence at 6 months or more than control participants (7.1% vs. 5.8%; RR, 1.28 [CI, 1.18 to 1.37]). However, no significant improvement was seen when nontailored materials were compared with no self-help materials (RR, 1.06 [CI, 0.98 to 1.16]), based on pooled analyses of 33 studies (*n* = 29 495) (22). A 2013 review on telephone counseling interventions found that recruiter-initiated telephone support improved rates of smoking cessation at 6 months or more (23). Based on pooled analyses of 12 studies (*n* = 30 182), abstinence rates were significantly higher in participants who received several counseling sessions via a telephone quit line than in those who received only a single session or self-help materials (10.7% vs. 7.6%; RR, 1.41 [CI, 1.20 to 1.66]). Pooled analyses of 51 studies (*n* = 30 246) found that recruiter-initiated telephone counseling that did not result from patients' calls to help lines also showed a benefit on smoking abstinence rates at 6 months or more compared with controls (13.1% vs. 9.7%; RR, 1.27 [CI, 1.20 to 1.36]).

The USPSTF also reviewed the 2008 Public Health Service guidelines on treating tobacco use and dependence for additional details on intensity and content of behavioral interventions, as well as type of staff providing counseling for smoking cessation (15). The USPSTF also considered evidence from additional reviews on mobile phone and Internet-based interventions (8). Although findings suggested a benefit, there were too few studies and the studies were too heterogeneous to draw definitive conclusions. The USPSTF also considered evidence from reviews on biomedical risk assessment interventions, exercise, and hypnotherapy for smoking cessation; the studies were too limited to draw conclusions (8). A 2014 review on the use of acupuncture for smoking cessation (9 studies; *n* = 1892) did not find increased rates of smoking cessation at 6 to 12 months (24).

Pharmacotherapy. The USPSTF reviewed 3 good-quality systematic reviews on pharmacotherapy for smoking cessation in nonpregnant adults (11).

A 2012 systematic review on NRT (117 studies; *n* = 51 265) (25) found that 17.3% of participants taking any form of NRT achieved abstinence at 6 months or more compared with 10.3% of participants receiving placebo or taking no NRT (RR, 1.60 [CI, 1.53 to 1.68]). Those who used 2 forms of NRT achieved higher abstinence rates than those who used just 1 (20.6% vs. 15.6%; RR, 1.34 [CI, 1.18 to 1.51]). All studies of dual NRT used the patch plus another type of NRT (such as gum, nasal spray, or inhaler), although which form served as the control varied. All single forms of NRT significantly improved cessation rates at 6 months or more (gum: RR, 1.49 [CI, 1.40 to 1.60]; patch: RR, 1.64 [CI, 1.52 to 1.78]; tablets or lozenges: RR, 1.95 [CI, 1.61 to 2.36]).

A 2014 systematic review on the use of antidepressants for smoking cessation (44 studies; *n* = 13 728) found that bupropion SR was associated with a significantly higher rate of smoking abstinence at 6 months or more than placebo or no bupropion SR (19.7% vs. 11.5%; RR, 1.62 [CI, 1.49 to 1.76]) (26).

Based on a smaller number of studies (14 studies; *n* = 6166), a 2012 systematic review (27) found that varenicline was associated with a higher cessation rate than placebo (28.0% vs. 12.0%; RR, 2.27 [CI, 2.02 to 2.55]).

Pooled analyses found that NRT plus bupropion was more effective than bupropion alone (RR, 1.24 [CI, 1.06 to 1.45]; 4 studies; *n* = 1991); however, it was not more effective than NRT alone (RR, 1.19 [CI, 0.94 to 1.51]; 12 studies) (8).

Smaller subsets of studies from these reviews directly compared types of pharmacotherapy for smoking cessation. Abstinence rates among participants using NRT versus bupropion SR at 6 months or more did not significantly differ (8 studies; *n* = 4086) (26). Two studies (*n* = 778) compared NRT and varenicline and found no significant difference between groups (27). Four studies evaluated bupropion SR versus varenicline; although not all of the studies found a significant difference, a pooled estimate (*n* = 1810) found a lower cessation rate with bupropion SR than varenicline (RR, 0.68 [CI, 0.56 to 0.83]).

Combinations of Behavioral Interventions and Pharmacotherapy. Combinations of behavioral counseling and pharmacotherapy for smoking cessation were also effective (8). A 2012 good-quality systematic review (40 studies; *n* = 15 021) (28) found that participants who received combination pharmacotherapy and intensive behavioral counseling had a higher abstinence rate at 6 months or more compared with control participants who received usual care, self-help materials, or brief advice on quitting (which was less intensive than the counseling or support given to the intervention groups) (14.5% vs. 8.3%; RR, 1.82 [CI, 1.66 to 2.00]). Most studies (27 of 40) used NRT as the pharmacotherapy and offered at least 4 behavioral counseling sessions (33 of 41). Another good-quality systematic review (29) found that abstinence rates at 6 months or more were higher in participants who received behav-

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ioral support as an adjunct to pharmacotherapy than in those who received pharmacotherapy alone (21.4% vs. 18.3%; RR, 1.16 [CI, 1.09 to 1.24]). Most studies (27 of 38) offered NRT alone as the pharmacotherapy. Participants in the control group may have also received some counseling or support, but it was less intensive than in the intervention group. Most studies (28 of 38) offered at least 91 minutes of total contact time, and many (16 of 38) offered greater than 300 minutes.

ENDS. The USPSTF identified only 2 fair-quality RCTs that reported on the effects of e-cigarettes for stopping conventional cigarette smoking (8). One study (30) of persons not attempting or wishing to quit found a higher abstinence rate at 12 months in participants using e-cigarettes than in control participants (11.0% vs. 4%; $P = 0.04$), whereas a larger study found no significant difference in abstinence rates at 6 months (31). Neither trial was conducted in the United States.

Pregnant Women

Behavioral Interventions. Based on a good-quality systematic review of 86 studies done in 2013 (8, 32), the USPSTF found that behavioral interventions in pregnant women (including behavioral counseling, feedback, health education, incentives, and social support) are effective at improving rates of smoking cessation as well as perinatal health outcomes. Compared with control participants (most often defined as usual care or less intensive interventions), pregnant women who received any type of behavioral intervention before the third trimester had higher cessation rates late in pregnancy (15.2% vs. 11.2%; RR, 1.45 [CI, 1.27 to 1.64]). Their children also had improved mean birthweight (mean difference, 40.78 g [CI, 18.45 to 63.10 g]), rates of low birthweight (RR, 0.82 [CI, 0.71 to 0.94]), and rates of preterm birth (RR, 0.82 [CI, 0.70 to 0.96]). When analyzed separately, behavioral counseling (the behavioral intervention in most studies) was effective in increasing abstinence rates in late pregnancy and mean birthweight in infants.

Pharmacotherapy. The USPSTF found a much smaller body of evidence on pharmacotherapy for smoking cessation in pregnant women. Only 5 RCTs ($n = 11\,922$) evaluating NRT use were found; there were no published trials on the use of bupropion SR or varenicline as an intervention for smoking cessation in pregnant women (8). The NRT studies reported very low (as low as <25%) adherence rates, which limited the interpretability of findings. Meta-analysis of these 5 trials showed no significant improvement in rates of smoking abstinence late in pregnancy (10.8% vs. 8.5%; RR, 1.24 [CI, 0.95 to 1.64]). Given the small number of studies that reported on perinatal health outcomes, meta-analysis was not done. Although results on preterm birth were mostly in the direction of benefit, only 1 study (33) showed a significant benefit. Reported results on mean birthweight and stillbirth were mixed. The largest trial ($n = 1050$) reported a higher rate of survival with no impairment at 2 years in children whose mothers received NRT during pregnancy (34).

Potential Harms of Interventions

Nonpregnant Adults

Behavioral Interventions. Evidence on harms of behavioral interventions for smoking cessation is limited. Based on the evidence reviewed by the USPSTF, only minor adverse events related to ear acupuncture, ear acupressure, and other auriculotherapy were identified. Adverse events related to other forms of behavioral interventions were not reported.

Pharmacotherapy. A 2014 fair-quality systematic review (35) of 21 studies ($n = 11\,647$) found that NRT use was associated with a higher rate of all cardiovascular adverse events (RR, 1.81 [CI, 1.35 to 2.43]) compared with placebo. This result seems to be driven by minor events, such as tachycardia and arrhythmia. No significant increase in major cardiovascular adverse events was found (RR, 1.38 [CI, 0.58 to 3.26]). An older fair-quality review from 2010 (36) also found higher rates of heart palpitation and chest pain, nausea and vomiting, gastrointestinal symptoms, and insomnia in NRT users than control participants. The patch was associated with an increase in skin irritation, and oral NRT was associated with throat soreness, mouth ulcers, and hiccups. Based on a subset of 8 studies, this older review also found no difference in mortality rates in participants using NRT versus control participants (odds ratio, 0.74 [CI, 0.33 to 1.67]).

The same systematic review also evaluated the potential harms of bupropion SR for smoking cessation (27 studies; $n = 10\,402$) (35). No significant difference was found between groups using bupropion SR versus placebo in all cardiovascular adverse events (RR, 1.03 [CI, 0.71 to 1.50]). A trend toward reduction in major cardiovascular adverse events was found in the bupropion SR group (RR, 0.57 [CI, 0.31 to 1.04]). A good-quality review (33 studies; $n = 9631$) found an increased rate of serious adverse events in bupropion SR users versus those using placebo or controls that was of borderline significance (RR, 1.30 [CI, 1.00 to 1.69]). On the basis of 19 studies, the current USPSTF review found no significant increase in serious psychiatric events with bupropion SR (RR, 0.60 [CI, 0.28 to 1.28]). It found 10 reported cases of seizures among 13 000 study participants. Bupropion SR labels include a boxed warning about serious neuropsychiatric events in persons who take bupropion SR for smoking cessation.

Concerns have been raised about varenicline and potential cardiovascular and neuropsychiatric harms. In 2012, the FDA issued a safety communication indicating a nonsignificant increase in major adverse cardiovascular events (37). Based on a fair-quality systematic review done in 2014 (35), a meta-analysis of 18 studies ($n = 9072$) showed no significant increase in all cardiovascular adverse events (RR, 1.24 [CI, 0.85 to 1.81]) or major cardiovascular adverse events (RR, 1.44 [CI, 0.73 to 2.83]). Varenicline labels contain a boxed warning about serious neuropsychiatric events; however, none of the evidence reviewed by the USPSTF reported on this outcome. A good-quality systematic review done in 2012 (27) found an increased risk for 1 or more serious adverse events in participants using varenicline compared with those receiving placebo (RR, 1.36 [CI, 1.03

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to 1.81]), but the type of serious adverse event was not specified. Most recently, the FDA issued a warning and approved updated labeling to describe a potential but rare occurrence of seizures with varenicline use and a potential interaction between varenicline and alcohol (38).

Combinations of Behavioral Interventions and Pharmacotherapy. The USPSTF did not identify any reports of adverse events related to combinations of behavioral interventions and pharmacotherapy.

ENDS. Neither of the 2 trials on e-cigarette use for conventional smoking cessation reported any serious adverse events related to product use or any difference in the frequency of adverse events (11). One study (30) reported a higher number of serious adverse events in the nicotine e-cigarette group (27 [19.7%]) than in the nicotine patch group (14 [11.8%]). However, the authors stated that they did not find any evidence on an association with the study product, and there was no difference in overall incidence of adverse events (serious and nonserious) between groups (incidence rate ratio, 1.05 [CI, 0.82 to 1.34]). Although it was not reported in the 2 trials, concerns have been raised about potentially harmful ingredients in e-cigarettes (11, 15). Because of the large number and variation of available devices and cartridge fluids and the lack of regulation, the toxicity and safety of e-cigarettes and ENDS are extremely difficult to determine uniformly (8). Inadvertent poisoning in children who mishandle nicotine cartridges is also a concern, and the number of calls to poison centers involving nicotine-containing e-cigarette liquids has increased from 1 per month in 2010 to 215 per month in 2014 (16). Based on estimates from a recent small survey, dual use of e-cigarettes and conventional cigarettes may be high: 9.4% of persons who smoke conventional cigarettes reported concurrently using e-cigarettes, and 76.8% of persons who use e-cigarettes reported concurrently smoking conventional cigarettes (39). Further research is needed to better understand how dual use of e-cigarettes and conventional cigarettes may affect attempts at cessation and initiation of smoking.

Pregnant Women

Behavioral Interventions. The USPSTF did not find any serious adverse events related to behavioral interventions for smoking cessation in pregnant women. According to 1 systematic review (32), an increase in smoking was reported in 4 out of 86 studies.

Pharmacotherapy. Evidence on harms from pharmacotherapy interventions for smoking cessation in pregnant women is limited. The USPSTF found no evidence of perinatal harms, although the number of studies was low and they were underpowered for rare outcomes (8). Similarly, there were too few studies to make any definitive determination on maternal harms of NRT. Maternal harms of NRT that have been reported in some studies include increased rates of cesarean delivery, slightly increased blood pressure (1 study reported an increase of 0.02 mm Hg per day in diastolic blood pressure over time [40]), and skin reaction to the NRT patch (8).

Estimate of Magnitude of Net Benefit

Nonpregnant Adults

Behavioral Interventions. The USPSTF found convincing evidence that behavioral interventions (such as physician and nurse advice, tailored self-help materials, and telephone counseling) provided or referred to by primary care providers substantially improve achievement of smoking cessation in nonpregnant adults. The USPSTF found adequate evidence that there are no harms of behavioral interventions. The USPSTF concludes with high certainty that the net benefit of providing behavioral interventions for smoking cessation in nonpregnant adults is substantial.

Pharmacotherapy. The USPSTF found convincing evidence that pharmacotherapy with NRT, bupropion SR, or varenicline substantially improves achievement of smoking cessation in nonpregnant adults. Evidence is also convincing that using 2 types of NRT moderately improves achievement of smoking cessation over single forms and that the addition of NRT to treatment with bupropion SR provides additional benefit over use of bupropion alone. The USPSTF found adequate evidence that the harms of pharmacotherapy, including serious cardiovascular adverse events and neuropsychiatric events, are small. It concludes with high certainty that the net benefit of providing pharmacotherapy for smoking cessation in nonpregnant adults is substantial.

Combinations of Behavioral and Pharmacotherapy Interventions. The USPSTF found convincing evidence that combinations of behavioral plus pharmacotherapy interventions substantially increase achievement of smoking cessation in nonpregnant adults. The USPSTF found adequate evidence that the harms of combined interventions are small. The USPSTF concludes with high certainty that the net benefit of providing combined interventions for smoking cessation in nonpregnant adults is substantial.

ENDS. The USPSTF concludes that the current evidence on the use of ENDS for conventional smoking cessation is insufficient. Evidence is lacking and conflicting, and the balance of benefits and harms cannot be determined. Given the established safety and effectiveness of behavioral and pharmacotherapy interventions, the USPSTF recommends that primary care providers direct patients who smoke to these other interventions.

Pregnant Women

Behavioral Interventions. The USPSTF found convincing evidence that behavioral interventions (such as behavioral counseling, feedback, health education, incentives, and social support) substantially improve achievement of smoking cessation in pregnant women, increase birthweight, and decrease preterm birth in their children. The USPSTF found convincing evidence that there are no harms of behavioral interventions and concludes with high certainty that the net benefit of providing behavioral interventions for smoking cessation in pregnant women is substantial.

Pharmacotherapy. The USPSTF concludes that the current evidence on pharmacotherapy for smoking ces-

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sation in pregnant women is insufficient. Evidence on NRT is limited and conflicting, evidence on other forms of pharmacotherapy is lacking, and the balance of benefits and harms cannot be determined.

Response to Public Comments

A draft version of this recommendation statement was posted for public comment on the USPSTF Web site from 5 May to 1 June 2015. Several comments requested clarification about which types of interventions are being recommended—pharmacotherapy, behavioral interventions, or combinations of both. Several comments also expressed concern that the draft language for the recommendation may cause clinicians to offer only 1 type of intervention. The USPSTF clarified that both intervention types (pharmacotherapy and behavioral interventions) are effective and recommended; combinations of interventions are most effective, and all should be offered. The best and most effective combinations are those that are acceptable to and feasible for an individual patient. Clinicians should consider the patient's specific medical history and preferences and offer and provide the combination that works best for that patient. Comments also sought clarification about which populations are included in the I statement for ENDS; the USPSTF clarified that the I statement for ENDS includes pregnant women. A few comments requested additional implementation resources. The USPSTF revised the recommendation to include a table that highlights effective components of behavioral interventions and provided links to additional resources on pharmacotherapy options and resources for pregnant women. The USPSTF revised its language on ENDS to reflect current terminology.

How Does Evidence Fit With Biological Understanding?

Because of the well-established health benefits of smoking cessation (1, 9), most of the research on interventions for smoking cessation focuses on cessation (rather than health outcomes) as a primary outcome. The current review identified 1 study of middle-aged men at high risk for cardiorespiratory disease that found a significantly smaller number of deaths from respiratory illness at 33 years of follow-up in participants who received advice from medical practitioners. The study also found favorable effects on all-cause mortality, coronary disease mortality, and lung cancer incidence and mortality at 20 years of follow-up, although these effects were not significant (41).

Update of Previous USPSTF Recommendation

In 2009, the USPSTF recommended that clinicians ask all adults about tobacco use and provide interventions for smoking cessation for those who use tobacco products (A recommendation) (42). It also recommended that clinicians ask all pregnant women about tobacco use and provide augmented, pregnancy-tailored counseling for those who smoke (A recommendation). The current recommendation updates and is consistent with the 2009 recommendation. In addition, the USPSTF reviewed evidence on ENDS, an emerging tobacco product, but found insufficient evidence to recommend for or against its use for smoking cessation. The USPSTF also reviewed updated evidence on pharmacotherapy interventions for smoking cessation in pregnant women and found that the evidence is still insufficient to make a recommendation.

Recommendations of Others

Numerous professional societies and health organizations, including the American College of Physicians (43), American College of Preventive Medicine (44), American Heart Association (45), and American Congress of Obstetricians and Gynecologists (46), recommend that clinicians screen for tobacco use and provide interventions to patients who smoke. More recently, with the emergence and increased use of e-cigarettes, some organizations have incorporated statements about e-cigarettes into their guidelines. Both the American Congress of Obstetricians and Gynecologists (46) and the American Heart Association (43) recommend that e-cigarettes be included in smoking screening questions. The American Heart Association also concludes that evidence is insufficient to counsel patients on the use of e-cigarettes as a primary cessation aid. The American Academy of Family Physicians has updated its recommendations, which are consistent with those of the USPSTF (47).

From the U.S. Preventive Services Task Force, Rockville, Maryland.

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Requests for Single Reprints: Reprints are available from the USPSTF Web site (www.uspreventiveservicestaskforce.org).

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Appendix: Members of the USPSTF

Members of the USPSTF at the time this recommendation was finalized† are Albert L. Siu, MD, MSPH, *Chair* (Mount Sinai School of Medicine, New York, and James J. Peters Veterans Affairs Medical Center, Bronx, New York); Kirsten Bibbins-Domingo, PhD, MD, MAS, *Co-Vice Chair* (University of California, San Francisco, San Francisco, California); David Grossman, MD, MPH, *Co-Vice Chair* (Group Health, Seattle, Washington); Linda Ciofu Baumann, PhD, RN, APRN (University of Wisconsin, Madison, Wisconsin); Karina W. Davidson, PhD, MASc (Columbia University, New York, New York); Mark Ebell, MD, MS (University of Georgia, Athens, Georgia); Francisco A.R. García, MD, MPH (Pima County Department of Health, Tucson, Arizona); Matthew Gillman, MD, SM (Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts); Jessica Herzstein, MD, MPH (Independent Consultant, Washington, DC); Alex R. Kemper, MD, MPH, MS (Duke University, Durham, North Carolina); Alexander H. Krist, MD, MPH (Fairfax Family Practice, Fairfax, and Virginia Commonwealth University, Richmond, Virginia); Ann E. Kurth, PhD, RN, MSN, MPH (New York University, New York, New York); Douglas K. Owens, MD, MS (Veterans Affairs Palo Alto Health Care System, Palo Alto, and Stanford University, Stanford, California); William R. Phillips, MD, MPH (University of Washington, Seattle, Washington); Maureen G. Phipps, MD, MPH (Brown University, Providence, Rhode Island); and Michael P. Pignone, MD, MPH (University of North Carolina, Chapel Hill, North Carolina). Former USPSTF member Susan Curry, PhD, also contributed to the development of this recommendation.

† For a list of current USPSTF members, visit www.uspreventiveservicestaskforce.org/Page/Name/our-members.

Appendix Table 1. What the USPSTF Grades Mean and Suggestions for Practice

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer/provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer/provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer/provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Appendix Table 2. USPSTF Levels of Certainty Regarding Net Benefit

Level of Certainty*	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: the number, size, or quality of individual studies; inconsistency of findings across individual studies; limited generalizability of findings to routine primary care practice; and lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: the limited number or size of studies; important flaws in study design or methods; inconsistency of findings across individual studies; gaps in the chain of evidence; findings that are not generalizable to routine primary care practice; and a lack of information on important health outcomes. More information may allow an estimation of effects on health outcomes.

* The USPSTF defines *certainty* as "likelihood that the USPSTF assessment of the net benefit of a preventive service is correct." The net benefit is defined as benefit minus harm of the preventive service as implemented in a general primary care population. The USPSTF assigns a certainty level on the basis of the nature of the overall evidence available to assess the net benefit of a preventive service.

[Intervention Review]

Acupuncture and related interventions for smoking cessation

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ABSTRACT

Background

Acupuncture and related techniques are promoted as a treatment for smoking cessation in the belief that they may reduce nicotine withdrawal symptoms.

Objectives

The objectives of this review are to determine the effectiveness of acupuncture and the related interventions of acupressure, laser therapy and electrostimulation in smoking cessation, in comparison with no intervention, sham treatment, or other interventions.

Search methods

We searched the Cochrane Tobacco Addiction Group Specialized Register (which includes trials of smoking cessation interventions identified from the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and PsycINFO) and AMED in October 2013. We also searched four Chinese databases in September 2013: Sino-Med, China National Knowledge Infrastructure, Wanfang Data and VIP.

Selection criteria

Randomized trials comparing a form of acupuncture, acupressure, laser therapy or electrostimulation with either no intervention, sham treatment or another intervention for smoking cessation.

Data collection and analysis

We extracted data in duplicate on the type of smokers recruited, the nature of the intervention and control procedures, the outcome measures, method of randomization, and completeness of follow-up.

We assessed abstinence from smoking at the earliest time-point (before six weeks) and at the last measurement point between six months and one year. We used the most rigorous definition of abstinence for each trial, and biochemically validated rates if available. Those lost to follow-up were counted as continuing smokers. Where appropriate, we performed meta-analysis pooling risk ratios using a fixed-effect model.

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The Return on Investment of a Medicaid Tobacco Cessation Program in Massachusetts

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Abstract

Background and Objective: A high proportion of low-income people insured by the Medicaid program smoke. Earlier research concerning a comprehensive tobacco cessation program implemented by the state of Massachusetts indicated that it was successful in reducing smoking prevalence and those who received tobacco cessation benefits had lower rates of in-patient admissions for cardiovascular conditions, including acute myocardial infarction, coronary atherosclerosis and non-specific chest pain. This study estimates the costs of the tobacco cessation benefit and the short-term Medicaid savings attributable to the aversion of inpatient hospitalization for cardiovascular conditions.

Methods: A cost-benefit analysis approach was used to estimate the program's return on investment. Administrative data were used to compute annual cost per participant. Data from the 2002–2008 Medical Expenditure Panel Survey and from the Behavioral Risk Factor Surveillance Surveys were used to estimate the costs of hospital inpatient admissions by Medicaid smokers. These were combined with earlier estimates of the rate of reduction in cardiovascular hospital admissions attributable to the tobacco cessation program to calculate the return on investment.

Findings: Administrative data indicated that program costs including pharmacotherapy, counseling and outreach costs about $183 per program participant (2010 $). We estimated inpatient savings per participant of $571 (range $549 to $583). Every $1 in program costs was associated with $3.12 (range $3.00 to $3.25) in medical savings, for a $2.12 (range $2.00 to $2.25) return on investment to the Medicaid program for every dollar spent.

Conclusions: These results suggest that an investment in comprehensive tobacco cessation services may result in substantial savings for Medicaid programs. Further federal and state policy actions to promote and cover comprehensive tobacco cessation services in Medicaid may be a cost-effective approach to improve health outcomes for low-income populations.

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Introduction

Smoking is a leading cause of preventable death in the United States, resulting in an estimated 450,000 annual premature deaths, or nearly one of every five deaths. It is responsible for roughly 30% of all cancer deaths, for nearly 80% of deaths from chronic obstructive pulmonary disease, and for early cardiovascular disease deaths [1–3]. More than one-third of the smoking-attributable years of potential life lost are related to cardiovascular disease [4]. The annual economic burden of smoking in the U.S. has been estimated at nearly $193 billion in direct medical costs and productivity losses [2]. While the life-time prevalence rate for adult smokers in the U.S. population is about 20% of this rate is about twice as high among adults insured by Medicaid [1–3]. Smoking-related medical costs are responsible for 11% of Medicaid expenditures, representing an estimated $22 billion in 2004 [5].

Federal policy has sought to reduce smoking by Medicaid beneficiaries as an important public health goal. For instance, one of the key objectives of Healthy People 2020 is to "increase comprehensive Medicaid insurance coverage of evidence-based treatment for nicotine dependency in States and the District of Columbia [6]." Considerable efforts have been made at the state level to reduce smoking. In 2009, Medicaid programs in 47 states and the District of Columbia offered at least some form of coverage for tobacco-dependence treatments, although most had a limited range of benefits [7]. The Patient Protection and Affordable Care Act will increase this coverage; it requires all states to offer comprehensive tobacco cessation services for pregnant women as of 2010 (Section 4107 of the Act) and to

State Medicaid Coverage for Tobacco Cessation Treatments and Barriers to Coverage — United States, 2014–2015

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Medicaid enrollees have a cigarette smoking prevalence (30.4%) twice as high as that of privately insured Americans (14.7%), placing them at increased risk for smoking-related disease and death (*1*). Individual, group, and telephone counseling and seven Food and Drug Administration (FDA)–approved medications are evidence-based, effective treatments for helping tobacco users quit (*2*). A *Healthy People 2020* objective (TU-8) calls for all state Medicaid programs to adopt comprehensive coverage of these treatments.* However, a previous *MMWR* report indicated that, although state Medicaid coverage of cessation treatments had improved during 2008–2014, this coverage was still limited in most states (*3*). To monitor the most recent trends in state Medicaid cessation coverage, the American Lung Association collected data on coverage of, and barriers to, accessing all evidence-based cessation treatments except telephone counseling† in state Medicaid programs (for a total of nine treatments) during January 31, 2014–June 30, 2015. As of June 30, 2015, all 50 states covered certain cessation treatments for at least some Medicaid enrollees. During 2014–2015, increases were observed in the number of states covering individual counseling, group counseling, and all seven FDA-approved cessation medications for all Medicaid enrollees; however, only nine states covered all nine treatments for all enrollees. Common barriers to accessing covered treatments included prior authorization requirements, limits on duration, annual limits on quit attempts, and required copayments. Previous research in both Medicaid and other populations indicates that state Medicaid programs could reduce smoking prevalence, smoking-related morbidity, and smoking-related health care costs among Medicaid enrollees by covering all evidence-based cessation treatments, removing all barriers to accessing these treatments, promoting coverage to Medicaid enrollees and health care providers, and monitoring use of covered treatments (*2,4–7*).

To assess state Medicaid tobacco cessation coverage, during August 2014–June 2015, the American Lung Association compiled data from Medicaid member websites and handbooks, Medicaid provider websites and handbooks, Medicaid policy manuals, preferred drug lists/formularies, and relevant regulations and legislation. Researchers searched for mentions of the nine cessation treatments considered in this study by using search functions on state Medicaid websites, other relevant state-sponsored websites, and the Google search engine. These data were then confirmed through consultations with staff members of state Medicaid agencies and health departments, or other knowledgeable state government personnel. Consultations were also used to supply missing documents and reconcile discrepancies. A state Medicaid program or managed care plan was only considered to cover a tobacco cessation treatment if documentation was available for this coverage. Information on state Medicaid cessation coverage compiled by the American Lung Association is available on the CDC State Activities Tracking and Evaluation (STATE) System, a database that contains tobacco-related epidemiologic and economic data and information on state tobacco-related legislation.§

As of June 2015, nine states (Connecticut, Indiana, Maine, Massachusetts, Minnesota, North Dakota, Ohio, Pennsylvania, and Vermont) cover all nine evidence-based cessation treatments considered in this study for all Medicaid enrollees, up from six states in January 2014.¶ Maine, North Dakota, and Ohio achieved this level of coverage during the study period. However, all nine states with this level of coverage have barriers, such as copayments (seven of nine states) or prior authorization requirements (seven of nine states), in place for some treatments. As of June 2015, 31 states covered individual counseling for all populations and plans (up from 27 in 2014), and 10 states covered group counseling for all populations and plans (up from seven in 2014) (Table 1). Additionally, 30 states covered all seven FDA-approved cessation medications for all populations and plans (up from 26 states in 2014) (Table 2). The most common barriers included prior authorization requirements (with 39 states reporting this barrier for at least certain populations or plans), limits on duration (38 states), annual limits on quit attempts (36 states), and required copayments (34 states) (Table 3).

* Additional information available at http://www.healthypeople.gov/2020/topics-objectives/topic/tobacco-use/objectives.

† Telephone counseling is available free to callers to state quitlines (including Medicaid enrollees) in all 50 states and the District of Columbia through the national quitline portal 1-800-QUIT-NOW, and therefore is not captured by this report. In June 2011, the Centers for Medicare and Medicaid Services announced that it would offer a 50% federal administrative match to state Medicaid programs for the cost of state quitline counseling provided to Medicaid enrollees.

§ Additional information available at http://www.cdc.gov/statesystem. Certain data presented in this report differ slightly from Medicaid cessation coverage data reported in the STATE System because of slightly different coding rules, categories, and reporting periods.

¶ Nevada was previously reported to cover all nine treatments considered in this report (*3*); however, researchers have since found that the Nevada Medicaid program does not cover group counseling.

TABLE 1. Medicaid coverage for tobacco cessation counseling, by state — United States, 2014–2015*,†

State	Individual counseling		Group counseling	
	2014	2015	2014	2015
Alabama	P	P	No	No
Alaska	Yes	Yes	No	No
Arizona	P	P	No	No
Arkansas	Yes	Yes	No	No
California	V	V	V	V
Colorado	P	P	P	P
Connecticut	Yes	Yes	Yes	Yes
Delaware	Yes	Yes	No	No
District of Columbia	Yes	NA	No	NA
Florida	V	V	V	V
Georgia	Yes	Yes	No	No
Hawaii	V	V	V	V
Idaho	No	Yes	No	No
Illinois	No	No	No	No
Indiana	Yes	Yes	Yes	Yes
Iowa	Yes	Yes	No	No
Kansas	P	P	P	P
Kentucky	V	V	V	V
Louisiana	No	No	V	V
Maine	Yes	Yes	No	Yes
Maryland	V	Yes	V	V
Massachusetts	Yes	Yes	Yes	Yes
Michigan	Yes	Yes	V	V
Minnesota	Yes	Yes	Yes	Yes
Mississippi	V	V	V	No
Missouri	Yes	Yes	No	No
Montana	Yes	Yes	No	No
Nebraska	Yes	Yes	V	No
Nevada	Yes	Yes	No§	No
New Hampshire	Yes	Yes	V§	V
New Jersey	No	Yes	No	No
New Mexico	V	Yes	V	No
New York	Yes	Yes	Yes	Yes
North Carolina	Yes	Yes	No	No
North Dakota	P	Yes	No	Yes
Ohio	V	Yes	V	Yes
Oklahoma	Yes	Yes	No	No
Oregon	Yes	Yes	V	V
Pennsylvania	Yes	Yes	Yes	Yes
Rhode Island	Yes	Yes	V	V
South Carolina	V	V	V	V
South Dakota	NA	P	NA	No
Tennessee	No	No	No	No
Texas	V	V	V	V
Utah	P	P	P	P
Vermont	Yes	Yes	Yes	Yes
Virginia	Yes	V	V	V
Washington	V	V	No	No
West Virginia	No	No	V	V
Wisconsin	Yes	Yes	V	V
Wyoming	Yes	Yes	No	No
Counts				
Yes	27	31	7	10
No	6	4	21	22
V	11	9	19	15
P	6	6	3	3
NA	1	1	1	1

Abbreviations: V = varies by plan; P = pregnant women only; NA = not available.
* Data as of January 31, 2014, and June 30, 2015.
† Because of differences in the methods and timing of data collection, certain findings differ from reports published before 2014 (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5941a4.htm).
§ Corrected from previous report.

Discussion

Although some progress in state Medicaid coverage of proven tobacco cessation treatments occurred during the study period, only nine states cover all nine treatments considered in this report for all Medicaid enrollees. Moreover, all of these states still have some barriers in place that make it more difficult for Medicaid enrollees to access these treatments, which would be expected to impede use of these treatments, quit attempts, and successful cessation (*2*). Removing these barriers increases access to and use of cessation treatments for both Medicaid enrollees and other populations (*2,5*). Comprehensive Medicaid tobacco cessation coverage with minimal barriers has the potential to help more Medicaid enrollees quit tobacco (*4,5*). Continued efforts by state Medicaid programs to increase coverage and use of evidence-based cessation treatments would be expected to result in improved health outcomes among Medicaid enrollees and reduced Medicaid health care costs (*6,7*).

Insurance coverage of evidence-based cessation treatments leads to increases in quit attempts, use of cessation treatments, and successful smoking cessation (*2*). One study determined that more comprehensive state Medicaid coverage for cessation treatments was associated with increased quit rates among smokers enrolled in Medicaid (*4*).

Effective January 2014, section 2502 of the 2010 Patient Protection and Affordable Care Act barred state Medicaid programs from excluding FDA-approved cessation medications from coverage.**,†† The Centers for Medicare and Medicaid Services has issued guidance to states on implementing this provision.§§,¶¶,*** This study finds that some states have improved their coverage of cessation medications during the study period. Other states might have improved this coverage

** Patient Protection and Affordable Care Act of 2010. Pub. L. No. 114–48 (March 23, 2010), as amended through May 1, 2010. Available at http://docs.house.gov/energycommerce/ppacacon.pdf.
†† Affordable Care Act provision section 4107 required state Medicaid programs to cover tobacco cessation counseling and pharmacotherapy for pregnant women with no cost-sharing, effective October 2010, which has resulted in increased state Medicaid coverage of cessation counseling and medications for pregnant women (*8*).
§§ Additional information available at http://www.medicaid.gov/medicaid-chip-program-information/by-topics/benefits/prescription-drugs/downloads/rx-releases/state-releases/state-rel-165.pdf.
¶¶ As of October 23, 2015, the Centers for Medicare and Medicaid Services had published State Plan Amendments from 36 states declaring that they have implemented this provision.
*** In addition to the Affordable Care Act provisions mentioned in this report, this legislation, as written, also provides strong incentives for all states to expand eligibility for Medicaid coverage. Although the Supreme Court ruling in June 2012 held that a state cannot lose federal funding for its existing Medicaid program if it does not participate in the expansion, 30 states and the District of Columbia have expanded Medicaid as of October 23, 2015 (http://kff.org/health-reform/slide/current-status-of-the-medicaid-expansion-decision). This is expected to further increase the number of smokers who have access to cessation treatments in expansion states; however, information for a comprehensive evaluation of cessation coverage in the Medicaid expansion population is not currently available.

TABLE 2. Medicaid coverage for tobacco cessation medications, by state — United States, 2014–2015*,†

	Nicotine patch		Nicotine gum		Nicotine lozenge		Nicotine nasal spray		Nicotine inhaler		Bupropion (Zyban)		Varenicline (Chantix)	
State	**2014**	**2015**	**2014**	**2015**	**2014**	**2015**	**2014**	**2015**	**2014**	**2015**	**2014**	**2015**	**2014**	**2015**
Alabama	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Alaska	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Arizona	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Arkansas	Yes	Yes	Yes	Yes	No	No	No	No	No	No	Yes	Yes	Yes	Yes
California	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Colorado	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Connecticut	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Delaware	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
District of Columbia	V	NA	V	NA	V	NA	No	NA	No	NA	No	NA	No	NA
Florida	V	Yes	V	Yes	V	Yes	V	No	V	No	V	Yes	V	Yes
Georgia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hawaii	Yes	Yes	Yes	Yes	V	V	V	V	V	V	V	V	V	V
Idaho	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Illinois	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Indiana	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Iowa	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kansas	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kentucky	Yes	Yes	V	V	V	V	V	V	V	V	V	V	V	V
Louisiana	Yes	V	Yes	V	V	V	V	V	V	V	Yes	Yes	V	V
Maine	P	Yes	P	Yes	P	Yes	P	Yes	P	Yes	P	Yes	P	Yes
Maryland	Yes	Yes	V	Yes	V	Yes	V	Yes	V	Yes	Yes	Yes	V	Yes
Massachusetts	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Michigan	Yes	Yes	Yes	Yes	V	Yes	V	V	V	Yes	Yes	Yes	Yes	Yes
Minnesota	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mississippi	Yes	Yes	Yes	Yes	Yes	Yes	V	V	V	V	Yes	Yes	Yes	Yes
Missouri	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Montana	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes
Nebraska	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Nevada	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
New Hampshire	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
New Jersey	Yes	Yes	Yes	Yes	V	Yes	V	Yes	V	Yes	Yes	Yes	V	Yes
New Mexico	Yes	Yes	Yes	Yes	Yes	Yes	Yes	V	Yes	V	Yes	V	Yes	Yes
New York	Yes	Yes	Yes	Yes	V	V	V	V	V	V	Yes	Yes	Yes	Yes
North Carolina	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
North Dakota	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ohio	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Oklahoma	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Oregon	Yes	V	V	V	V	V	V	V	V	V	Yes	V	Yes	V
Pennsylvania	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Rhode Island	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
South Carolina	Yes	Yes	V	Yes	V	V	V	V	V	V	V	V	V	V
South Dakota	P	P	P	P	P	P	No	No	No	No	NA	Yes	NA	Yes
Tennessee	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Texas	Yes	Yes	Yes	Yes	No	Yes	No	No	No	No	Yes	Yes	Yes	Yes
Utah	V	V	V	V	V	V	V	V	V	V	Yes	Yes	Yes	Yes
Vermont	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Virginia	Yes	Yes	V	V	V	V	V	V	V	V	Yes	V	V	V
Washington	V	V	V	V	V	V	V	V	V	V	V	V	V	V
West Virginia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Wisconsin	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wyoming	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Yes
Counts														
Yes	45	45	40	43	30	38	28	32	29	33	43	43	38	42
No	0	0	0	0	5	2	8	6	7	6	1	0	2	1
V	4	4	9	6	14	9	14	12	14	11	5	7	9	7
P	2	1	2	1	2	1	1	0	1	0	1	0	1	0
NA	0	1	0	1	0	1	0	1	0	1	1	1	1	1

Abbreviations: V = varies by plan; P = pregnant women only; NA = not available.

* Data as of January 31, 2014, and June 30, 2015.

† Because of differences in the methods and timing of data collection, certain findings differ from reports published before 2014 (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5941a4.htm).

TABLE 3. Barriers to Medicaid coverage for tobacco cessation treatments, by state — United States, 2014 and 2015*,†,§

State	Copayments required		Prior authorization required		Counseling required for medications		Stepped-care therapy		Limits on duration		Annual limit on quit attempts		Lifetime limit on quit attempts	
	2014	2015	2014	2015	2014	2015	2014	2015	2014	2015	2014	2015	2014	2015
Alabama	Yes¶	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	No
Alaska	Yes	Yes	No	Yes	No	No	No	No	Yes	Yes	Yes	Yes	No	No
Arizona	No	No	No	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No
Arkansas	No	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	No
California	No	No	V	V	V	No	V	V	V	V	V	V	No	No
Colorado	V	V	Yes	Yes	V	V	No	No	Yes	Yes	Yes	Yes	No	No
Connecticut	No	No	Yes	Yes	No	No	No	No	Yes	Yes	Yes	No	No	No
Delaware	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	No
District of Columbia	No	NA	No	NA	No	NA	No	NA	V	NA	No	NA	No	NA
Florida	V	V	V	V	V	No	V	V	V	V	V	V	V	V
Georgia	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Hawaii	V	V	V	V	V	V	V	V	V	V	Yes	Yes	No	No
Idaho	No	No	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	No	No
Illinois	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	No
Indiana	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Iowa	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Kansas	No	No	No	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No
Kentucky	No	V	V	V	V	V	No	No	V	V	V	V	No	No
Louisiana	Yes	Yes	No	V	V	V	No	No	V	V	No	No	No	No
Maine	No	No	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	No	Yes	No
Maryland	V	V	V	V	V	V	V	V	V	V	V	V	V	No
Massachusetts	Yes	Yes	Yes	Yes	No	No	No	No	No	No	Yes	Yes	No	No
Michigan	V	No	V	V	V	No	V	V	V	V	V	Yes	No¶	No
Minnesota	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	No
Mississippi	Yes	V	No	No	No	No	No	No	V	Yes	No	No	No	No
Missouri	No	No	Yes	Yes	No	No	No	No	Yes	Yes	No	No	Yes	Yes
Montana	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Nebraska	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	No
Nevada	Yes	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Yes	No	No
New Hampshire	Yes	Yes	Yes¶	Yes	No	No	No	No	No	No	Yes	Yes	No	No
New Jersey	V	V	V	V	No	No	No	No	V	V	V	V	V	V
New Mexico	No	No	V	V	No	V	No	No	V	V	V	V	No	No
New York	V	V	V	V	No	No	No	No	Yes	Yes	Yes	Yes	No	No
North Carolina	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	No	No	No	No
North Dakota	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	No
Ohio	V	Yes	V	V	No	No	V	V	V	No	No	No	No	No
Oklahoma	Yes	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	No	No
Oregon	V	No	V	V	V	V	No	No	V	V	V	V	No	No
Pennsylvania	Yes	Yes	V	V	No	No	No	No	Yes	Yes	Yes	No	No	No
Rhode Island	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
South Carolina	V	V	V	V	V	V	V	V	Yes	Yes	V	V	No	No
South Dakota	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	No
Tennessee	No	No	Yes	Yes	No	No	No	Yes	Yes	No	No	Yes	No	No
Texas	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	No
Utah	Yes	Yes	Yes	Yes	No	No	No	No	No	No	No	No	No	No
Vermont	Yes	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Yes	No	No
Virginia	V	V	V	V	No	V	V	V	V	V	V	V	No	No
Washington	No	No	V	V	V	V	No	No	V	V	V	V	V	V
West Virginia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Wisconsin	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	No
Wyoming	Yes	Yes	No	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No
Counts														
Yes	25	24	22	23	12	10	8	11	25	26	27	26	2	1
No	15	16	14	11	28	30	35	31	11	12	13	14	45	46
V	11	10	15	16	11	10	8	8	15	12	11	10	4	3
P	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NA	0	1	0	1	0	1	0	1	0	1	0	1	0	1

Abbreviations: V = varies by plan; P = pregnant women only; NA = not available.

* Data as of January 31, 2014, and June 30, 2015.

† Because of differences in the methods and timing of data collection, certain findings differ from reports published before 2014 (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5941a4.htm).

§ Barriers apply to one or more cessation treatments.

¶ Corrected from previous report.

before the study period in response to this provision. State Medicaid programs can maximize the effect of this provision on cessation by placing tobacco cessation medications on preferred drug lists (or similar documents), removing barriers to accessing these medications, and adding notices of coverage to public plan documents (*9*). State Medicaid programs can also increase cessation among Medicaid enrollees by covering cessation counseling along with cessation medications, because the combined use of these treatments is more effective in increasing quit rates than the use of either alone (*2*).

The findings in this report are subject to at least four limitations. First, 2015 data were not available for the District of Columbia. Second, in cases where official documents were not publicly available or conflicted with one another, knowledgeable state government personnel were consulted to provide non-public documentation or resolve discrepancies; this information might have been inaccurate in some cases. Third, cessation coverage can vary widely across Medicaid managed care plans, making it difficult to determine the coverage provided by specific plans in practice. Finally, this report does not assess promotion, awareness, or use of state Medicaid cessation coverage. The extent to which smokers use covered treatments is a key factor in determining the effect of cessation coverage, and promotion and awareness of coverage in turn determine the level of use. Although examining these factors is important to accurately evaluate the impact of a state's Medicaid cessation coverage, this type of data is not currently available in most states. It is important to identify an approach to obtain information on use of cessation treatments by Medicaid enrollees.

Although state Medicaid cessation coverage improved during 2014–2015, coverage still falls substantially short of the *Healthy People 2020* target of full coverage in all 50 states and the District of Columbia; almost six million Medicaid enrollees continue to smoke cigarettes (*1*). Smoking-related diseases accounted for approximately 15% of annual Medicaid spending during 2006–2010, amounting to more than $39 billion per year (*10*).

State Medicaid programs can maximize tobacco cessation among Medicaid enrollees by covering all evidence-based cessation treatments, removing barriers that impede access to these treatments, promoting their coverage to Medicaid tobacco users and health care providers, and monitoring use of covered treatments (*5*–*7*). State Medicaid programs that take these actions have the potential to substantially reduce tobacco use, tobacco-related disease, and health care costs among Medicaid enrollees.

Summary

What is already known on this topic?

Medicaid enrollees smoke cigarettes at a higher rate than privately insured U.S. residents. Comprehensive state Medicaid cessation coverage has the potential to reduce smoking, smoking-related disease, and health care costs among Medicaid enrollees. Although state Medicaid coverage of cessation treatments had improved during 2008–2014, this coverage was still limited in most states.

What is added by this report?

Although state Medicaid cessation coverage improved during 2014–2015, coverage continues to fall substantially short of the *Healthy People 2020* target of full coverage in all 50 states and the District of Columbia. As of June 2015, only nine states cover all nine evidence-based cessation treatments considered in this study for all Medicaid enrollees, up from six states in 2014. All of these states have barriers to accessing some treatments.

What are the implications for public health practice?

State Medicaid programs can help more Medicaid enrollees quit tobacco use by covering all evidence-based cessation treatments, removing barriers that make it difficult for enrollees to access these treatments, promoting cessation coverage, and monitoring use of covered treatments. State Medicaid programs can enhance the effect of the Affordable Care Act provision barring state Medicaid coverage from excluding cessation medications by placing these medications on preferred drug lists, removing barriers to accessing these medications, and covering cessation counseling as well as medications.

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[1]American Lung Association; [2]Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, CDC.

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Tobacco use disorder and elective surgery

Question: Should a guideline be adopted about tobacco cessation and elective surgery?

Question source: QHOC Medical Directors

Issue: There are poorer healing outcomes associated with patients who actively use tobacco products who are undergoing surgery. The QHOC Medical Directors are interested in whether the evidence suggests specific criteria for poorer outcomes which may lead to coverage decisions about elective surgeries.

Current Prioritized List Status

GUIDELINE NOTE 100, SMOKING AND SPINAL FUSION
Lines 51,154,204,258,374,412,484,533,588
Non-emergent spinal arthrodesis (CPT 22532-22634) is limited to patients who are non-smoking for 6 months prior to the planned procedure. Patients should be given access to appropriate smoking cessation therapy.

GUIDELINE NOTE 112, LUNG VOLUME REDUCTION SURGERY
Line 288
Lung volume reduction surgery (LVRS, CPT 32491, 32672) is included on Line 288 only for treatment of patients with radiological evidence of severe bilateral upper lobe predominant emphysema (diagnosis code ICD-10-CM J43.9/ICD-9-CM 492.0, 492.8) and all of the following:

1. BMI ≤31.1 kg/m2 (men) or ≤32.3 kg/m 2 (women)
2. Stable with ≤20 mg prednisone (or equivalent) dose a day
3. Pulmonary function testing showing
   a. Forced expiratory volume in one second (FEV 1) ≤ 45% predicted and, if age 70 or older, FEV 1≥ 15% predicted value
   b. Total lung capacity (TLC) ≥ 100% predicted post-bronchodilator
   c. Residual volume (RV) ≥ 150% predicted post-bronchodilator
4. PCO 2, ≤ 60 mm Hg (PCO 2, ≤ 55 mm Hg if 1-mile above sea level)
5. PO 2, ≥ 45 mm Hg on room air (PO 2, ≥ 30 mm Hg if 1-mile above sea level)
6. Post-rehabilitation 6-min walk of ≥ 140 m
7. Non-smoking for 6 months prior to surgery, as shown by cotinine level

The procedure must be performed at an approved facility (1) certified by the Joint Commission on Accreditation of Healthcare Organizations (Joint Commission) under the LVRS Disease Specific Care Certification Program or (2) approved as Medicare lung or heart-lung transplantation hospitals. The patient must have approval for surgery by pulmonary physician, thoracic surgeon, and anesthesiologist post-rehabilitation. The patient must have approval for surgery by cardiologist if any of the following are present: unstable angina; left-ventricular ejection fraction (LVEF) cannot be estimated from the echocardiogram; LVEF <45%; dobutamineradionuclide cardiac scan indicates

coronary artery disease or ventricular dysfunction; arrhythmia (>5 premature ventricular contractions per minute; cardiac rhythm other than sinus; premature ventricular contractions on EKG at rest).

GUIDELINE NOTE 8, BARIATRIC SURGERY
Lines 30,594
…Excerpt

> Must remain free of abuse of or dependence on alcohol during the six-month period immediately preceding surgery. No current use of nicotine or illicit drugs and must remain abstinent from their use during the six-month observation period. Testing will, at a minimum, be conducted within one month of the surgery to confirm abstinence from nicotine and illicit drugs.

Line: 5
Condition: TOBACCO DEPENDENCE (See Guideline Notes 4,64,65)
Treatment: MEDICAL THERAPY/BRIEF COUNSELING NOT TO EXCEED 10 FOLLOW-UP VISITS OVER 3 MONTHS
ICD-9: 305.1,649.00-649.04
CPT: 96127-96154,97810-97814,98966-98969,99078,99201-99215,99224,99324-99350,99366,99406,99407,99441-99449,99487-99498,99605-99607
HCPCS: D1320,G0425-G0427,G0436,G0437,G0459,G0463,G0466,G0467,G0469, G0470,G9016,H0038,S9453

GUIDELINE NOTE 4, TOBACCO DEPENDENCE
Line 5
Persons are eligible for tobacco dependence counseling if a documented quit date has been established.

Evidence Summary

MED, 2013 Report

Clinical review:
There are many studies linking perioperative smoking with surgical complications and poor post-operative outcomes (such as wound healing, cardiac and pulmonary complications, and death). There is also associated longer hospital stays, need for revision, and increased health care costs.

Current medical literature is abundant with studies that demonstrate perioperative smoking is strongly linked to surgical complications and poor post-operative outcomes. Adverse post-operative outcomes include impaired wound and tissue healing, and cardiopulmonary complications such as respiratory failure, cardiac arrest, and myocardial infarction (Balaji 2008; Centers for Medicare and Medicaid Services [CMS] 2013; Finks 2011; Katznelson 2011; Khullar 2013; Rinker 2013; Safadi 2009; Turan 2011).

Additionally, smokers may be up to twice as likely to experience pneumonia, unplanned intubation, mechanical ventilation, and death after surgery due to preoperative smoking (Khullar 2013). These outcomes can often result in the need for prolonged hospital stays, and the potential for surgical revision (Katznelson 2011; Turan 2011). They may put active smokers at higher risk for surgical complications, and elevate healthcare costs over time (CMS 2013; Khullar 2013; Turan 2011).

Perioperative smoking has been shown to adversely affect outcomes associated with a wide range of surgeries including cardiac, vascular, thoracic, general, urologic, and plastic reconstructive procedures (Katznelson 2011; Turan 2011).

Thomsen, 2014 (not included in packet due to study's length)

1. Cochrane systematic review of preoperative smoking cessation interventions
2. 13 trials involving 2010 participants
3. Overall quality of evidence moderate due to small sample size
4. Intensive interventions appeared to reduce any complications (RR 0.42; 95% CI 0.27 to 0.65, 2 trials, 210 participants) and on wound complications (RR 0.31; 95% CI 0.16 to 0.62, 2 trials, 210 participants). For brief interventions, where the impact on smoking had been smaller, there was no evidence of a reduction in complications (RR 0.92; 95% CI 0.72 to 1.19, 4 trials, 493 participants) for any complication (RR 0.99; 95% CI 0.70 to 1.40, 3 trials, 325 participants) for wound complications. The trial of varenicline did not detect an effect on postoperative complications (RR 0.94; 95% CI 0.52 to 1.72, 1 trial, 286 participants).
    a. Intensive interventions were defined as multisession face to face counseling
    b. Intensive interventions were effective at cessation at the time of surgery (pooled risk ratio (RR) 10.76; 95% confidence interval (CI) 4.55 to 25.46, two trials, 210 participants) than for brief interventions (RR 1.30; 95% CI 1.16 to 1.46, 7 trials, 1141 participants).
    a. A single trial did not show evidence of benefit of a scheduled reduced smoking intervention.
5. Conclusions: preoperative smoking interventions providing behavioural support and offering NRT increase short-terms smoking cessation and may reduce postoperative morbidity. One trial of varenicline begun shortly before surgery has shown a benefit on long-term cessation but did not detect an effect on early abstinence or on postoperative complications. The optimal preoperative intervention intensity remains unknown. Based on indirect comparisons and evidence from two small trials, interventions that begin four to eight weeks before surgery, include weekly counselling and use of NRT, are more likely to have an impact on complications and on long-term smoking cessation.

Khullar, 2012.

1. Clinical review on impact of smoking on surgical procedures

2. Most trials have found that 4 to 8 weeks of smoking abstinence substantially reduces perioperative complications and the need for repeat surgery

Sorenson, 2012

1. Systematic review and metanalysis
2. 140 cohort studies including 479,150 patients
3. Results: The pooled adjusted odds ratios (95% CI) were 3.60 (2.62-4.93) for necrosis, 2.07 (1.53-2.81) for healing delay and dehiscence, 1.79 (1.57-2.04) for surgical site infection, 2.27 (1.82-2.84) for wound complications, 2.07 (1.23-3.47) for hernia, and 2.44 (1.66-3.58) for lack of fistula or bone healing. Former smokers and patients who never smoked were compared in 24 studies including 47,764 patients, and former smokers and current smokers were compared in 20 studies including 40,629 patients. The pooled unadjusted odds ratios were 1.30 (1.07-1.59) and 0.69 (0.56-0.85), respectively, for healing complications combined. In 4 randomized controlled trials, smoking cessation intervention reduced surgical site infections (odds ratio, 0.43 [95% CI, 0.21-0.85]), but not other healing complications (0.51 [0.22-1.19]).

Corbett, 2012

1. Clinical review of tobacco cessation and solid organ transplantation
2. 1996 Consensus guidelines from US and Europe state that candidates for lung transplantation must have been free of substance addiction (including alcohol, tobacco, and narcotics) for at least 6 months. More recently, they have changed to make smoking a relative contraindication
3. In heart transplantation, smokers have:
    a. Reduced life expectance, increased rates of coronary artery disease, increased malignancy, increased all cause and cardiac death, postoperative renal dysfunction, longer hospital stays, skin cancer. And other solid organ cancers. Limits life expectance.
4. In kidney transplantation smokers have:
    a. Increased rates of allograft loss, death, transplant failure, diabetes, cardiovascular events, and cancer
5. In liver transplantation smokers have:
    a. increased overall mortality, cardiovascular-related mortality, and sepsis-related mortality, and biliary complication rates
    b. one conflicting single center study exists

NICE Guideline - Osteoarthritis: Care and Management in Adults. Patient-specific factors (including age, sex, smoking, obesity and comorbidities) should not be barriers to referral for joint surgery. **[2008, amended 2014]**

Other state policies:

- Alabama requires patients to be tobacco free for 8 weeks prior to gastric bypass surgery
- West Virginia requires patients to be tobacco free for 6 months prior to gastric bypass surgery
- Other states (Washington, California, and Louisiana) have more vague language about being substance free, which may or may not include tobacco

Other Payers

Aetna

(2012) – Heart-Lung Transplantation – smokers must be abstinent for three months before consideration for candidacy;

(2013a) – Lung Transplantation – smokers must be abstinent for six months before consideration for candidacy;

(2013b) – Obesity Surgery – patients suggested to stop smoking six to eight weeks before surgery;

(2013c) – Pulmonary Rehabilitation – candidate must not have a recent history of smoking and/or has quit for at least three months;

(2013d) – Spinal Surgery: Laminectomy and Fusion – no specified discontinuation time, but cites smoking as an absolute contraindication that would preclude a patient from eligibility; and

(2013e) – Surgical/Penile Revascularization for Erectile Dysfunction – patient must not be actively smoking (no time limits specified).

BlueCross BlueShield (Anthem; Alabama) o Anthem BCBS (2012) – identifies smoking as a major contraindication/risk factor for electrical bone growth stimulation.

Alabama BCBS (2012) – requires patients to be tobacco-free for a minimum of eight weeks prior to surgery for bariatric procedures.

Cigna lists tobacco-free policies on two procedures:

(2007) – Lumbar Fusion for Spinal Instability and Degenerative Disc Conditions – smoking identified as a major contraindication and associated with risk of pseudoarthritis; and

(2009) – Lung Volume Reduction Surgery – smoking cessation required for at least six months.

UniCare (2012) – has tobacco-free policies for lung volume reduction surgery requiring candidates to be abstinent from smoking for at least four months.

HERC Staff Assessment

There is a strong association with smoking and increased morbidity with surgical procedures. The Prioritized List currently has restrictions on surgery requiring smoking cessation for at least 6 months for lung volume reduction surgery, bariatric surgery, and for spinal fusion. Other elective surgeries may result in improved post-surgical outcomes with similar smoking cessation requirements based on limited evidence. NICE specifically recommends not having smoking status being a barrier to joint replacement referral. There are effective interventions to improve cessation rates that are covered for OHP.

HERC Staff Recommendations:

1) Continue requiring smoking cessation 6 months prior to lung volume reduction surgery, bariatric surgery, and spinal fusion.
2) Consider adding the following Guideline Note, but given the limited evidence, could be a recommendation rather than a requirement (which may be confusing).

   ANCILLARY GUIDELINE NOTE XXX, SMOKING CESSATION AND ELECTIVE SURGICAL PROCEDURES

   Intensive smoking cessation interventions (multiple face to face behavioral counseling +/- nicotine replacement) in active tobacco users are recommended/required at least 4-8 weeks prior to elective surgical procedures.

   Certain procedures, such as lung volume reduction surgery, bariatric surgery, and spinal fusion have 6 month tobacco abstinence requirements.

3) Do not add a requirement for transplantation. While there is certainly evidence of poorer outcomes associated with smoking and transplant, these criteria are managed by the transplant centers and through OARs; a guideline note may be redundant and/or unnecessary.

The Impact of Smoking on Surgical Outcomes

Dhruv Khullar, BA, John Maa, MD, FACS

Smoking substantially increases a patient's risk of surgical complications. Despite this, almost half of all surgeons do not routinely counsel their patients to stop smoking before an operation. Studies show that although up to 75% of smokers who undergo surgery would like to quit, only about 5% will stop smoking permanently around the time of elective surgery. The intent of this article is to raise surgeon awareness of the deleterious impact of smoking on surgical outcomes and emphasize the unique opportunity in the teachable moment of surgery to enable patients to succeed in their efforts to quit smoking.

Toll of smoking on surgical care and need for action

Smoking is the leading preventable cause of morbidity and mortality in the United States. It is associated with a number of chronic conditions, including cancer, coronary artery disease, chronic obstructive pulmonary disease, cerebrovascular disease, and peripheral vascular disease. Despite major advances in tobacco control in the 20th century, 44 million Americans continue to smoke and 1 in 5 deaths in the United States can be attributed to tobacco use.[1] Each year, smoking causes nearly 440,000 deaths in the United States, which by comparison, is more than HIV, illegal drug use, alcohol use, motor vehicle accidents, and suicides combined.[2] It is estimated that the societal costs of tobacco use amount to $96 billion in medical expenses and $97 billion in lost productivity annually.[2] In addition to the tremendous toll on the health of the American people, smoking places a considerable burden on an already strained US health care system, diminishing our ability to contain costs, expand access, and improve quality.

Smoking has long been identified as a risk factor for chronic disease, but a growing body of evidence suggests that it is also an independent risk factor for surgery. Because this association was first described in 1944,[3] more than 300 studies have examined the association between smoking and surgical outcomes.[4] Active smoking is clearly linked to an increased risk of perioperative cardiovascular, pulmonary, and wound healing complications, including infections, anastomotic dehiscence, reintubation, and respiratory failure. These complications in turn result in longer hospital stays, higher rates of ICU admission, greater need for repeat surgery, and higher overall costs of care. Smoking at the time of surgery is also associated with inferior long-term surgical outcomes and decreased overall patient satisfaction with the procedure.

Importantly, even brief preoperative smoking cessation can substantially reduce the risk of complications, and there are a number of effective interventions to help patients stop smoking. Studies show that 75% of patients would like to quit smoking,[5] and that scheduling of elective surgery provides a unique opportunity to help smokers quit in the long term.[6] However, we are currently not doing enough to seize this teachable moment. Patients are often poorly informed of the benefits of smoking cessation for surgical outcomes[7,8] and unaware of available resources for quitting.[9]

In addition to the adverse health consequences, a substantial financial cost is associated with these surgical complications. One study estimates that the pulmonary complications associated with perioperative smoking result in an additional cost of $52,000 per surgical episode.[10] At a time when our nation is struggling to curb health costs and maintain quality of care, increased emphasis on perioperative smoking cessation holds great promise. As first-hand witnesses of the enormous burden of tobacco use, frontline clinicians should take a proactive stand to reduce the health care costs associated with active smoking. A key next step in smoking cessation efforts is to involve surgeons to a greater degree in perioperative cessation activities. Given the power of the teachable moment and the long-term health benefits to patients, surgeons should seize any opportunity to help their patients quit smoking, without fearing that brief preoperative abstinence could worsen outcomes. Specifically, surgeons should identify patients who smoke, provide access to intensive smoking-cessation interventions, and insist on complete abstinence before operating, particularly for nonessential, elective procedures. The goal of this article is to highlight the existing scientific data about the impact of smoking on surgical outcomes, and to suggest ways that surgeons in particular can lead the efforts nation-

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Sørensen 2012 Abstract

Sørensen LT[1]. Wound healing and infection in surgery. The clinical impact of smoking and smoking cessation: a systematic review and meta-analysis. Arch Surg. 2012 Apr;147(4):373-83. doi: 10.1001/archsurg.2012.5.

Objectives To clarify the evidence on smoking and postoperative healing complications across surgical specialties and to determine the impact of perioperative smoking cessation intervention.

Data Sources Cohort studies and randomized controlled trials.

Study Selection Selected studies were identified through electronic databases (CENTRAL, MEDLINE, and EMBASE) and by hand searching.

Data Extraction Multiple data on study characteristics were extracted. Risk of bias was assessed by means of the Newcastle-Ottawa Scale and Jadad score. Healing outcome was classified as necrosis, healing delay and dehiscence, surgical site infection, wound complications, hernia, and lack of fistula or bone healing. Mantel-Haenszel and inverse variance methods for meta-analysis (fixed- and random-effects models) were used.

Data Synthesis Smokers and nonsmokers were compared in 140 cohort studies including 479 150 patients. The pooled adjusted odds ratios (95% CI) were 3.60 (2.62-4.93) for necrosis, 2.07 (1.53-2.81) for healing delay and dehiscence, 1.79 (1.57-2.04) for surgical site infection, 2.27 (1.82-2.84) for wound complications, 2.07 (1.23-3.47) for hernia, and 2.44 (1.66-3.58) for lack of fistula or bone healing. Former smokers and patients who never smoked were compared in 24 studies including 47 764 patients, and former smokers and current smokers were compared in 20 studies including 40 629 patients. The pooled unadjusted odds ratios were 1.30 (1.07-1.59) and 0.69 (0.56-0.85), respectively, for healing complications combined. In 4 randomized controlled trials, smoking cessation intervention reduced surgical site infections (odds ratio, 0.43 [95% CI, 0.21-0.85]), but not other healing complications (0.51 [0.22-1.19]).

Conclusions Postoperative healing complications occur significantly more often in smokers compared with nonsmokers and in former smokers compared with those who never smoked. Perioperative smoking cessation intervention reduces surgical site infections, but not other healing complications.

Tobacco Smoking and Solid Organ Transplantation

Chris Corbett,[1,2] *Matthew J. Armstrong,*[1,2] *and James Neuberger*[1,3]

Smoking, both by donors and by recipients, has a major impact on outcomes after organ transplantation. Recipients of smokers' organs are at greater risk of death (lungs hazard ratio [HR], 1.36; heart HR, 1.8; and liver HR, 1.25), extended intensive care stays, and greater need for ventilation. Kidney function is significantly worse at 1 year after transplantation in recipients of grafts from smokers compared with nonsmokers. Clinicians must balance the use of such higher-risk organs with the consequences on waiting list mortality if the donor pool is reduced further by exclusion of such donors. Smoking by kidney transplant recipients significantly increases the risk of cardiovascular events (29.2% vs. 15.4%), renal fibrosis, rejection, and malignancy (HR, 2.56). Furthermore, liver recipients who smoke have higher rates of hepatic artery thrombosis, biliary complications, and malignancy (13% vs. 2%). Heart recipients with a smoking history have increased risk of developing coronary atherosclerosis (21.2% vs. 12.3%), graft dysfunction, and loss after transplantation. Self-reporting of smoking is commonplace but unreliable, which limits its use as a tool for selection of transplant candidates. Despite effective counseling and pharmacotherapy, recidivism rates after transplantation remain high (10–40%). Transplant services need to be more proactive in educating and implementing effective smoking cessation strategies to reduce rates of recidivism and the posttransplantation complications associated with smoking. The adverse impact of smoking by the recipient supports the requirement for a 6-month period of abstinence in lung recipients and cessation before other solid organs.

Keywords: Smoking, Transplant, Nicotine, Tobacco, Cigarettes.

(*Transplantation* 2012;94: 979–987)

Smoking is well recognized to increase the risks of a wide range of pathologies, including cardiovascular disease, stroke, peripheral vascular disease, peptic ulcer disease, lung disease, and cancer (*1*). Smoking has also been shown to be a major risk factor for bacterial and viral infections (*2*) as well as the development of chronic kidney disease (*3*). Most notably, smoking increases the risk of all-cause mortality and contributes to approximately 5 million premature deaths per year (*4*). In 2000, smoking accounted for 4.83 million deaths worldwide (*5*). Based on prevalence figures of 30%, the World Health Organization has estimated that smoking will kill 8 million people a year by 2030 (*6*).

The adverse effects of smoking on outcomes after surgical procedures (*7*), particularly solid organ transplantation, are well documented. After liver transplantation, smoking increases all-cause mortality, with cardiovascular and sepsis accounting for the majority of deaths (*8*). In kidney and heart recipients, smoking is associated with graft loss (*9*) and delayed graft function (*10*).

Smoking cessation should always be advocated by clinicians and indeed is mandatory for 6 months before lung transplantation (*11*). As will be discussed in detail below, use of organs from donors who have smoked has a negative impact on the outcomes after transplantation (*12*).

This review summarizes the documented effects of tobacco smoking on solid organ transplantation, with particular focus on the impact of donor and recipient smoking on posttransplantation morbidity and mortality. The impact of smoking cessation and the efficacy of interventions to reduce smoking rates are also reviewed.

An evidence-based approach was used for this review. MEDLINE search was performed to February 2012 using the following terms: smoking (or tobacco), transplant, smoking detection, and smoking cessation. Literature for this review was selected from a total of 153 publications.

PATHOLOGIC EFFECTS OF TOBACCO SMOKING

Tobacco smoking affects multiple organ systems in the human body, impairing both psychologic and physical well-being and are summarized in other reviews and Figure 1.

CURRENT GUIDELINES ON SMOKING AND ORGAN TRANSPLANTATION

In 1998, the American Society for Transplant Physicians, the American Thoracic Society, the European Respiratory

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Section 7.0

Coverage Guidances

Value-based Benefits Subcommittee Coverage Guidance Summary

Oregon Health Evidence Review Commission

August 13, 2015

Oregon Health Authority

OREGON HEALTH & SCIENCE UNIVERSITY

Center For Evidence-based Policy

Coverage Guidance

For VbBS review and approval

- Planned Out-of-Hospital Birth

Planned Out-of-Hospital Birth

Planned Out-of-Hospital Birth Process Overview

- Initial search – Trusted sources (Aug 2014)
- EbGS – 9/2014, 11/2014, 2/2015, 4/2015, 6/2015
  - New Search (April/May 2015)
    - Medline – 617 citations reviewed
    - Public Comment / Expert Testimony – 20 citations
- Extensive Public Comment (13 commenters)
  - Add/Modify/Delete Table

Planned Out-of-Hospital Birth
Clinical Background

- Planned out-of-hospital birth
  - Home
  - Birth center
- Direct entry midwives
  - Must be licensed as of January 2015
- Oregon statistics (2012)
  - 4.8% (2,021) of 42,011 live term births were planned OOH
  - 4.0/1,000 (planned Out-of-Hospital Birth) vs 2.1/1,000 (hospital) perinatal mortality rate

Planned Out-of-Hospital Birth
Initial Search – Primary Evidence Sources

Olsen, O., & Clausen, J. A. (2012). Planned hospital birth versus planned home birth. *Cochrane Database of Systematic Reviews, 9*. Accessed August 9, 2014, from http://almenpraksis.ku.dk/nyheder/oleolsen/Hjemmef_dsel.pdf

National Institute for Clinical Excellence (2014). *Intrapartum care: Care of healthy women and their babies during childbirth. Clinical Guideline 190,* December 2014. Accessed December 15, 2014, from https://www.nice.org.uk/guidance/cg190/resources/guidance-intrapartum-care-care-of-healthy-women-and-their-babies-during-childbirth-pdf

Planned Out-of-Hospital Birth
Initial Search – Additional Evidence Sources

- Cochrane (2000)
- College of Midwives of British Columbia (2014)
- College of Midwives of Ontario (2015)
- de Jonge (2009)
- Dowswell (1996)
- Hendrix (2009)
- Hodnett (2009)
- Hutton (2009)
- Jansen (2009)
- Netherlands Ministry of Health, Welfare, and Sport (n.d.)
- Oregon Health Authority (2013)
- Wax (2010)
- Zeitlin (n.d.)

Planned Out-of-Hospital Birth
New Search – Additional Evidence Sources

- Birthplace in England Collaborative Group (2011) (*very low*)*
- Catling-Paull (2013) (*very low*)
- Cheng (2013) (*very low*)
- Cheyney (2014) *(low)*
- Davis (2012) (*very low*)
- Jassen (2009) (*very low*)
- de Jonge (2015) (*very low*)
- de Jonge (2013) (*very low*)
- de Jonge (2009) (*very low*)
- Hutton (2009) (*very low*)
- Johnson (2005) (*very low*)
- Kennare (2010) (*very low*)
- Nove (2012) (*very low*)
- Stapleton (2013) (*very low*)
- van der Kooy (2011) (*very low*)

* *Indicates study quality based on GRADE*

Planned Out-of-Hospital Birth Evidence Summary

- Predominately observational studies
- Potential for indirectness
  - Direct entry midwife vs certified midwife or certified nurse midwife
  - Systems of care (Australia, Canada, Netherlands, UK)
  - Regulatory and training requirements
- Population-based studies
- Focus on critical and important outcomes
  - Perinatal mortality
  - Neonatal mortality
  - Cesarean rate
  - Postpartum hemorrhage

Planned Out-of-Hospital Birth Evidence Summary

Source	Study Design (n)	Location	Results* (home vs hospital)
Birthplace, 2011	Prospective cohort (16,840)	England	C-Section 2.8% vs 11.1% (obstetric unit) Composite outcome(neonatal) 4.2% vs 4.4% (obstetric unit)
Catling-Paull, 2013	Retrospective cohort (1,807)	Australia	C-Section 5.4% (home) Perinatal mortality (fetal to 7d) 1.7/1000 (home)
Cheng, 2013	Retrospective cohort (12,039)	US	*No critical or important outcomes reported*
Cheyney, 2014	Prospective cohort (16,924)	US	C-section 5.2% (home) Perinatal mortality 2.06/1000 (home)

* Only critical and important outcomes listed

Planned Out-of-Hospital Birth Evidence Summary

Source	Study Design (n)	Location	Results* (home vs hospital)
Davis, 2011	Retrospective cohort (1,830)	New Zealand	Postpartum hemmorrhage adjOR 0.93 (95% CI 0.49 – 1.74)
de Jonge, 2009	Retrospective cohort (466,041)	Netherlands	Perinatal mortality adjRR 1.00 (95% CI 0.78 – 1.27)
de Jonge, 2013	Retrospective cohort (92,333)	Netherlands	Composite outcome (maternal) 1.5/1000 vs 2.7/1000
de Jonge, 2015	Retrospective cohort (335,683)	Netherlands	Perinatal mortality (nulliparous) adjOR 0.99 (95% CI 0.79 – 1.24) Perinatal mortality (multiparous) adjOR 1.16 (95% CI 0.87 – 1.55)
Hutton, 2009	Retrospective cohort (6,692)	Canada	C-section RR 0.64 (95% CI 0.56 – 0.73) Perinatal mortality 0.13% vs 0.12%

* Only critical and important outcomes listed

Planned Out-of-Hospital Birth Evidence Summary

Source	Study Design (n)	Location	Results* (home vs hospital)
Janssen, 2009	Retrospective cohort (2,889)	Canada	C-section adjRR 0.76 (95% CI 0.64 – 0.91) Perinatal mortality RR 0.61 (95% CI 0.06 – 5.88)
Johnson, 2005	Retrospective cohort (5,418)	US	C-section 3.7% (home) Perinatal mortality 2.03/1000 (home)
Kennere, 2009	Retrospective cohort (1,141)	Australia	C-section adjOR 0.27 (95% CI 0.22 – 0.34) Perinatal mortality adjOR 1.38 (95% CI 0.56 – 3.41)
Nove, 2012	Retrospective cohort (5,598)	England	Postpartum hemorrhage adjOR 0.40 (95% CI 0.26 – 0.59)

* Only critical and important outcomes listed

Planned Out-of-Hospital Birth Evidence Summary

Source	Study Design (n)	Location	Results* (home vs hospital)
Stapleton, 2013	Retrospective cohort (15,574)	US	C-section 6.1% (home) Perinatal mortality 0.87/1000 (birth center)
van der Kooy, 2011	Retrospective cohort (402,912)	Netherlands	Perinatal mortality adjRR 1.05 (95% CI 0.91 – 1.21)

* Only critical and important outcomes listed

Planned Out-of-Hospital Birth
Public Comment Summary

- Proposed high risk criteria, transfer criteria, or consultation criteria modifications
  - Additions
    - Prior Cesarean section (*clarified criteria intent to be excluded*)*
    - Ultrasound between 12-30 weeks (*no addition*)
    - Diabetes, pre-existing or gestational (*added to consultation and high risk criteria*)
    - Having had an IUD (*no addition*)
    - Extremes of maternal age (*no addition*)
    - Prior 3rd degree laceration (*added to consultation criteria*)
    - Prior fractured clavicle and shoulder dystocia (*added to consultation criteria*)

** EbGS Subcommittee actions in italics*

Planned Out-of-Hospital Birth
Public Comment Summary

- Proposed risk criteria modifications
  - Additions (cont)
    - Maternal Jehovah's Witness status (*no addition*)
    - Maternal seizure disorder / epilepsy (*removed from high risk criteria, added to consultation criteria*)
    - Prior infant > 9 lbs (*added to consultation criteria*)
    - Suspected macrosomia (*added to consultation criteria*)
    - Incomplete prenatal testing (e.g., strep, STI, GDM) (*added to consultation criteria, unknown HIV/HBV added to high risk criteria*)
    - Severe mental health issues not well-controlled (*maternal mental illness requiring inpatient care added to high risk criteria, maternal mental illness under outpatient care added consultation criteria*)

Planned Out-of-Hospital Birth
Public Comment Summary

- Proposed risk criteria modifications
  - Additions (cont)
    - Written transfer plan in effect that accepting OB and pediatrician agree with (*no change, not included in box language*)
    - History of blood clot or bleeding disorder (*added to risk criteria*)
    - History of a group B Strep septic infant (*no addition*)
    - Substance abuse, including marijuana (*added to risk criteria, clarified language*)
    - Primiparity (*no addition*)

Planned Out-of-Hospital Birth
Public Comment Summary

- Proposed risk criteria modifications
  - Modifications
    - 36 and 41+ weeks gestational age definition (*clarified criteria*)
    - Placenta previa, vasa previa, low lying placenta (*clarified criteria*)
    - Small for gestation age fetus (*clarified criteria*)
    - Fetal growth retardation (*clarified criteria*)
    - Genital herpes (*clarified criteria*)
    - Retained placenta > 1 hr (*clarified criteria*)
    - Maternal hemoglobin < 11 (*clarified criteria*)
    - Pregnancy-inducted hypertension, pre-existing hypertension (*clarified criteria*)
    - Thrombopenia (*clarified criteria*)

Planned Out-of-Hospital Birth
Public Comment Summary

- Proposed risk criteria modifications
  - Modifications (cont)
    - Chorioamnionitis or other serious infection with fever > 38 C (*no change to chorioamniontitis criteria, added fever as an independent transfer criteria*)
  - Deletions
    - Prior 4th degree laceration (*added to consultation and risk criteria*)
    - Intrapartum 3rd or 4th degree laceration *(added to consultation and risk criteria*)
    - Intrapartum or postpartum complications (*no change*)
    - History of preterm birth (*no deletion*)
    - History of more than 3 first trimester spontaneous abortions, or > 1 second trimester spontaneous abortion (*no deletion*)

Planned Out-of-Hospital Birth
Public Comment Summary

- Proposed risk criteria modifications
  - Deletions (cont)
    - Failure to progress / failure of head to engage in active labor (*no deletion*)
    - Cervical dysplasia (*no deletion*)
    - Hyperemesis gravidarum (*no deletion, language clarified*)
    - Family history of genetic / heritable disorders (*no deletion*)
    - History of pre-eclampsia / HELLP syndrome (*no deletion, language clarified*)
    - History of unexplained stillbirth / neonatal death or previous death related to intrapartum difficulty (*no deletion, language clarified*)
    - History of postpartum hemorrhage requiring additional treatment or blood transfusion (*changed from risk to consultation criteria)*

Planned Out-of-Hospital Birth
Public Comment Summary

- Proposed risk criteria modifications
  - Deletions (cont)
    - History of retained placenta requiring manual removal (*no deletion*)
    - Confirmed intrauterine death (*consultation criteria*)
    - BMI at first prenatal visit of greater than 35 kg/m^2 (*no deletion*)
    - Prelabor rupture of membranes > 24 hrs (*no deletion*)
    - Thick meconium staining of amniotic fluid (*added to risk criteria*)
    - Retained placenta (*no deletion*)
    - Blood group incompatibility (*clarified criteria*)

Planned Out-of-Hospital Birth
Box Language

- *Please refer to Coverage Guidance for*
  - *Box language*
  - *GRADE Table*

From VbBS Minutes 10/1/2015

- **Topic: Coverage Guidance—Planned Out-of-hospital births**

  Discussion: Livingston presented the process overview, evidence summary and core issues addressed by public comment. Dr. Duncan Neilson was introduced as an appointed expert. He is the Clinical Vice President of surgical services of Legacy health system and an obstetrician/gynecologist. Dr. Neilson reviewed the history of this effort beginning with a legislative mandate that involved licensing direct entry midwives as of January 2015 and an Oregon Health Authority Licensed Direct Entry Midwifery Workgroup that recommended that HERC evaluate the evidence and update the appropriate risk criteria to try to ensure safe and effective planned out-of-hospital births.

  The subcommittee discussed that these risk criteria are about coverage. A woman with risk criteria may choose to have a planned out-of-hospital birth, but this would not be covered by the Oregon Health Plan. There was an amendment made to the box language to clarify that the intent is about coverage.

  Livingston proceeded to discuss the options, being explicit about which criteria needed to be ruled out and also allowing for ambiguity when certain criteria may remain unknown if there were not clinical suspicion that would indicate a workup was appropriate. The example of ultrasound was discussed and the subcommittee agreed that it would be necessary to rule out certain risk criteria. Livingston highlighted some of the risk criteria that had received more public comment as well as some suggestions for clarifying language.

  There was a discussion as to whether lethal congenital anomalies with planned nonrescucitation would be appropriate for coverage in an out-of-hospital birth setting. Kim Wentz stated that there are times when the prenatal diagnosis is wrong or the parents change their mind when the baby is born. Neilson stated that there are some lethal congenital anomalies that are more black and white and others that are gray. Also, in some cases it may be more explicit that nonresuscitation is clearly appropriate and changes in diagnosis or management plans are highly unlikely. There was a discussion about preserving the autonomy of the mother if the fetus doesn't require treatment. Anencephaly was given as an example. After discussion the subcommittee decided to move the revised language including "nonresuscitation planned" to be a criterion requiring consultation.

  There was a discussion of a series of criteria that may not be known if there was no clinical suspicion, but also needing to define what those clinical factors may be. In a discussion about intrauterine growth reduction (IUGR), initially there was a proposal to define concerning clinical signs such as fundal height <3 cm from estimated gestational age over two measurements; however, Neilson suggested that other factors besides

fundal height may be important and the estimation of fetal weight is multimodal. The language was changed to state that serial fundal measurements are required, but not to define what exactly suspicion for IUGR would entail. It was concluded that both serial blood pressure measurements and serial fundal heights would be required in order to verify the absence or presence of this high risk criteria.

There was a discussion of the unknown syphilis, HIV, or Hepatitis B status and a proposal to add "positive" status to the coverage exclusion criteria. Members discussed whether appropriate care could be given to a positive mother in a home setting and they decided that given the potential risk to the fetus/infant and the potential for intervention, that these would be risk criteria that would exclude a woman from coverage. Syphilis was added based on a staff recommendation as a result of recent public health data showing an increase in syphilis in Oregon.

Pollack commented and others agreed that readability of the box language would be improved with categorizing of the risk conditions.

Public comment:

> Jeannie Stagner, CNM, of Klamath Falls. She stated she has been a midwife for 33 years, starting as direct entry midwife and later serving as a consultant to the Arizona State Department of Health Services. She stated she does not have hospital privileges and has a licensed birth center. She expressed concerns that inadequate stakeholder representation was involved in the process, and that guidelines are attempting to change midwifery statutes. She stated that 100% of her patients would have been found ineligible according to consultation guidelines, specifically raising concerns about VBAC and women receiving outpatient mental health care. She also raised concerns about the availability of consultants, especially in rural communities.

Neilson reviewed the history of this process starting with the legislation, the development of the licensed direct entry midwifery workgroup, including involvement of stakeholders with midwifery representation, and how the HERC work results from those processes.

The subcommittee discussed revising the language around maternal mental illness. Pollack suggested requiring consultation in cases where there is suspicion for psychosis or self-harm. The subcommittee ran out of further discussion time.

There was a discussion about the word "compliance" and the feeling it invokes. It was clarified that this will serve as the basis for rules and compliance would be an appropriate choice of words.

Summary of changes agreed to prior to the end of the meeting:

- Clarify further that these high risk criteria relate to coverage

- Move life-threatening congenital anomalies (unless fatal anomalies with nonresuscitation planned) to consultation criteria
- Add that serial fundal height measurements and serial blood pressure measurements are required
- Add unknown, or positive, syphilis, HIV, or hepatitis B status to high risk coverage exclusion criteria
- Categorize risk conditions in box language to improve readability
- Discuss further modifying the language on maternal mental illness requiring outpatient psychiatric care

Discussion to continue at the November 12, 2015 VbBS/HERC meetings.

From HERC Minutes 10/1/2015

Coverage Guidance Topic: Planned Out-of-hospital Birth
Meeting materials, pages 236-406

Livingston presented the proposed coverage guidance from EbGS. VbBS was unable to complete its review during the morning's meeting, therefore this presentation was informational.
Livingston explained that planned OOH births (OOHB) include birthing at home and in a birthing center. The evidence, which has a potential for indirectness from various factors such as systems of care, licensure and regulatory requirements, came from predominately observational studies from other countries (Australia, Canada, Netherlands, UK). The studies were population-based and focused on perinatal mortality, neonatal mortality, cesarean rate and postpartum hemorrhage.

Saha said this is an issue where there were strong opinions on both side, an uncommon situation. In opposition, hospitals and OB/GYNs and citizens all advocated against it because of the higher infant mortality rate. As great as the out-of-hospital birth movement sounds, there have been many problems. In support, largely the midwifery community, contended they can provide the care and restrictions should be loosened so they can be paid for their services. He said this topic is the most contentious issue the Commission has faced: If families decided to go against the set guidelines and restrictions, should the health plan be responsible for the health related consequences that can arise?

Livingston said the OHA, who have been involved with this topic, has the Licensed Direct Entry Midwifery Workgroup addressing multiple issues related to out of hospital birth. Currently, births outside a hospital setting are being paid for under "fee-for-service" rather than through the Coordinated Care Organizations (CCOs). Livingston went on to say that the Health Systems Division (formerly DMAP) and CCO medical directors have asked HERC to be extremely explicit with coverage criteria.

There was some discussion around "informed consent;" it may be the mother's right to give birth outside a hospital. Others countered the health system should pay for only the safest and most effective care. Others in the healthcare field shared that many times they have seen informed consent forms signed *after* procedures.

Saha explained one issue that makes this contentious is there was evidence presented that OOHB was just as safe as hospital birth. There was come contrary evidence as well. Patient selection becomes an issue in these studies. In-hospital births will always be stacked with the higher complexity births that you would expect to have worse outcomes because the complexity causes someone who might have otherwise had an OOHB to have an in-hospital birth; accounting for risk-adjustment is often imperfect. The second issue is the best studies came out of Europe (the Netherlands), where the networking system between OOHB delivery

providers and in-hospital delivery providers is very strong. If something goes wrong, the woman can briskly be transported to the hospital; the communication between the midwife in the home and the OB/GYN in the hospital is very strong. That is not necessarily the case in the United States. We cannot expect the same level of safety.

Livingston reviewed the GRADE-Informed Framework (page 272). There was no discussion. She then began to review the Box language components, which are four pages long.

High risk criteria examples in the proposal VbBS is reviewing (no out-of-hospital coverage):

- Cesarean section or other hysterotomy (vaginal birth after Cesarean (VBAC))
- Unexplained stillbirth/neonatal death or previous death related to intrapartum difficulty
- Baby with neonatal encephalopathy
- Gestational age - preterm or postdates (defined as gestational age < 37 weeks + 0 days or > 41 weeks + 6 days)
- Pre-existing chronic hypertension
- Pregnancy-induced hypertension with diastolic blood pressure greater than or equal to 90 mmHg or systolic blood pressure greater than or equal to 140 mmHg on two consecutive readings taken at least 30 minutes apart
- Multiple gestations

Livingston clarified the risk of vaginal birth after Cesarean (VBAC) is death since uterine rupture occurs suddenly, not allowing time for transfer to a hospital. Hodges said some rural hospitals in Oregon stopped allowing that even in a hospital setting because they were unable to get adequate malpractice insurance. Agreeing it can be dangerous, Livingston added that when it occurs it will be catastrophic for the mother, the baby or both, and there is no way to accurately predict which birth is likely to be the one.

Transfer criteria examples being reviewed

- Uterine rupture, inversion or prolapse
- Hemorrhage (hypovolemia, shock, need for transfusion)
- Retained placenta > 60 minutes
- Non-cephalic fetal presentation
- Eclampsia or pre-eclampsia
- Placental abruption/abnormal bleeding
- Certain serious infections

Consultation criteria examples being reviewed:

- More than three first trimester spontaneous abortions, or more than one second trimester spontaneous abortion
- Blood group incompatibility, and/or Rh sensitization
- Pre-eclampsia, not requiring preterm birth
- More than one preterm birth, or preterm birth less than 34 weeks 0 days in most recent pregnancy

- Cervical insufficiency/prior cerclage

Life threating fatal anomalies
Livingston said some feedback given involved the situation where a baby is not expected to survive due to a pre-birth diagnosis of a fatal anomaly. Families sometime choose to give birth in the home, to allow for bonding time before the infant passes away. In those cases the families opt for non-resuscitation. She reports concerns from others thatsometimes the pre-diagnosis is wrong and sometime the parents change their minds and want resuscitation, which may not be possible in a home setting. VbBS discussed changing births of this type to fall under the proposed consultation criteria instead of a high risk coverage exclusion criteria, because in some cases it is clear that nonviability will occur and nonresuscitation may be fully appropriate

Livingston gave a summary of VbBS member's struggles with implementation. EbGS did not delve into implementation details. However, explicit requests from those who would implement these recommendations necessitated VbBS members needing to identify which conditions must explicitly be known and which tests must absolutely be required for coverage. Chan added this is the most granular coverage guidance we have written to date; he feels perhaps it borders on a clinical guideline. The core of the guidance is to ensure the risks are low enough so there is no unnecessary risks to the child and no extra costs to the health system. Saha agreed and went on to say when there is a condition is a common as pregnancy there is likely going to be long extensive list of permissible and not permissible circumstances. Some community objections center around the "consultation criteria" because in some areas it is hard to get consultations and there are some places where a midwife cannot order an ultrasound because the radiology group is unwilling to take on the risk. Saha added someone who wants to have OOHB is unlikely to want to have many tests and that is fine; the health system just will not pay for the delivery if is unable to confirm that the pregnancy is low-risk.

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: PLANNED OUT-OF-HOSPITAL BIRTH

DRAFT for VbBS/HERC meeting materials 11/12/15

HERC COVERAGE GUIDANCE

Planned out-of-hospital (OOH) birth is recommended for coverage for women who do not have high-risk coverage exclusion criteria as outlined below *(weak recommendation)*. This coverage recommendation is based on the performance of appropriate risk assessments[1] and the OOH birth attendant's compliance with the consultation and transfer criteria as outlined below.

Planned OOH birth is not recommended for coverage for women who have high risk coverage exclusion criteria as outlined below, or when appropriate risk assessments are not performed, or where the attendant does not comply with the consultation and transfer criteria as outlined below *(strong recommendation)*.

High-risk coverage exclusion criteria:

Complications in a previous pregnancy:

Maternal surgical history

- Cesarean section or other hysterotomy
- Uterine rupture
- Retained placenta requiring surgical removal
- Fourth-degree laceration without satisfactory functional recovery

Maternal medical history

- Pre-eclampsia requiring preterm birth
- Eclampsia
- HELLP syndrome

Fetal

- Unexplained stillbirth/neonatal death or previous death related to intrapartum difficulty
- Baby with neonatal encephalopathy
- Placental abruption with adverse outcome

Complications of current pregnancy:

Maternal

- Induction of labor
- Prelabor rupture of membranes > 24 hours
- Pre-existing chronic hypertension; Pregnancy-induced hypertension with diastolic blood pressure greater than or equal to 90 mmHg or systolic blood pressure greater than or equal to 140 mmHg on two consecutive readings taken at least 30 minutes apart
- Eclampsia or pre-eclampsia
- Anemia – hemoglobin less than 8.5 g/dL
- Thrombosis/thromboembolism/ thrombocytopenia (platelets <100,000), or other maternal bleeding disorder
- Drug or alcohol use with high risk for adverse effects to fetal or maternal health
- Maternal mental illness requiring inpatient care
- Unknown HIV or Hepatitis B status
- Current active infection of varicella at the time of labor; rubella infection anytime during pregnancy; active infection (outbreak) of genital herpes at the time of labor
- Refractory hyperemesis gravidarum
- Diabetes, type I or II, uncontrolled gestational diabetes, or gestational diabetes controlled with medication

Placental

- Low lying placenta within 2 cm or less of cervical os at term; placenta previa, vasa previa
- Placental abruption/abnormal bleeding
- Recurrent antepartum hemorrhage
- Uteroplacental insufficiency

Fetal

- Gestational age - preterm or postdates (defined as gestational age < 37 weeks + 0 days or > 41 weeks + 6 days)
- Multiple gestation
- Non-cephalic fetal presentation
- IUGR (defined as fetal weight less than fifth percentile using ethnically-appropriate growth tables, or concerning reduced growth velocity on ultrasound)
- Abnormal fetal heart rate/Doppler/surveillance studies
- Oligohydramnios or polyhydramnios
- Blood group incompatibility with atypical antibodies, or Rh sensitization
- ~~Life-threatening congenital anomalies (unless non-rescucitation planned)~~
- Molar pregnancy

Transfer criteria:

If out-of-hospital birth is planned, certain intrapartum and postpartum complications may necessitate transfer to a hospital to meet coverage criteria. For these indications, an attempt should be made to transfer the mother and/or her newborn; however, imminent fetal delivery may delay or preclude actual transfer prior to birth.

Maternal

- Temperature ≥ 38.0 C
- Maternal infection (endometritis, UTI, wound, breast)
- Hemorrhage (hypovolemia, shock, need for transfusion)
- Retained placenta > 60 minutes
- Laceration requiring hospital repair (e.g., extensive vaginal, cervical or third- or fourth-degree trauma)
- Enlarging hematoma
- Bladder or rectal dysfunction
- ~~Thrombophlebitis/thromboembolism~~
- ~~Pregnancy-induced hypertension with diastolic blood pressure greater than or equal to 90 mmHg or raised systolic blood pressure greater than or equal to 140 mmHg on two consecutive readings taken at least 30 minutes apart~~
- ~~Anemia – hemoglobin less than 8.5 g/dL~~
- ~~Current active infection of varicella at the time of labor~~
- ~~Current active infection (outbreak) of genital herpes at the time of labor~~
- ~~Eclampsia or pre-eclampsia~~

Fetal and uteroplacental

- Repetitive or persistent abnormal fetal heart rate pattern
- Thick meconium staining of amniotic fluid
- Prolapsed umbilical cord
- Failure to progress/failure of head to engage in active labor
- Chorioamnionitis or other serious infection (including toxoplasmosis, rubella, CMV, HIV, etc.)
- Uterine rupture, inversion or prolapse
- ~~Non-cephalic fetal presentation~~
- ~~Placental abruption/abnormal bleeding~~

If the infant is delivered out-of-hospital, the following complications require transfer to a hospital for the out-of-hospital birth to meet coverage criteria:

- Low Apgar score (< 5 at 5 minutes, < 7 at 10 minutes)
- Weight less than 5th percentile for gestational age

- Unexpected significant or life-threatening congenital anomalies
- Respiratory or cardiac irregularities, cyanosis, pallor
- Temperature instability, fever, suspected infection or dehydration
- Hyperglycemia/hypoglycemia unresponsive to treatment
- Hypotonia, tremors, seizures, hyperirritability
- Excessive bruising, enlarging cephalohematoma, significant birth trauma
- Vomiting/diarrhea

Consultation criteria:

Certain high risk conditions require consultation (by a provider of maternity care who is credentialed to admit and manage pregnancies in a hospital) for coverage of a planned out-of-hospital birth to be recommended. These complications include (but are not limited to) patients with:

Complications in a previous pregnancy:

Maternal

- More than three first trimester spontaneous abortions, or more than one second trimester spontaneous abortion
- More than one preterm birth, or preterm birth less than 34 weeks 0 days in most recent pregnancy
- Pre-eclampsia, not requiring preterm birth
- Cervical insufficiency/prior cerclage
- Third degree laceration; fourth-degree laceration with satisfactory functional recovery
- Postpartum hemorrhage requiring additional pharmacologic treatment or blood transfusion
- Retained placenta requiring manual removal

Fetal

- Child with congenital and/or hereditary disorder
- Baby > 4.5 kg or 9 lbs 14 oz
- Shoulder dystocia, with or without fetal clavicular fracture
- Unexplained stillbirth/neonatal death or previous death unrelated to intrapartum difficulty
- ~~Perinatal death~~
- Unresolved intrauterine growth restriction (IUGR) or small for gestational age (defined as fetal or birth weight less than fifth percentile using ethnically-appropriate growth tables)
- Blood group incompatibility, and/or Rh sensitization

Complications of current pregnancy:

Maternal

- Inadequate prenatal care (defined as less than five prenatal visits or care began in the third trimester)
- Body mass index at first prenatal visit of greater than 35 kg/m^2
- History of maternal seizure disorder (excluding eclampsia)
- Gestational diabetes, diet-controlled
- Maternal mental illness under outpatient psychiatric care (with suspicion for psychosis or potential harm to self or infant) under
- Maternal anemia with hemoglobin < 10.5 g/dL
- Third-degree laceration not requiring hospital repair
- Laparotomy during pregnancy
- ~~Cervical dysplasia requiring evaluation *~~

Fetal

- Fetal macrosomia (estimated weight >4.5 kg or 9 lbs 14 oz)
- Confirmed intrauterine death
- Life-threatening congenital anomalies (unless non rescucitation planned)
- Family history of genetic/heritable disorders that would impact labor, delivery or newborn care

[1]Risk assessment should be done initially when planning the location of birth, and updated throughout pregnancy, labor, and delivery to determine if out-of-hospital birth is still appropriate *(weak recommendation).*

Note: Definitions for strength of recommendation are provided in Appendix B GRADE Element Description

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Heath Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

EVIDENCE SOURCES

[Note: an additional source search was done at the request of the Evidence-based Guidelines Subcommittee (EbGS) at their April 2, 2015 meeting. A narrative and tabular description of this additional evidence follows that of the initial evidence sources description. A complete listing of the sources included from the new search immediately follows those identified in the initial search below. A full evidence table for these new sources is included in Appendix C.]

Initial search – trusted sources

Olsen, O., & Clausen, J. A. (2012). Planned hospital birth versus planned home birth. *Cochrane Database of Systematic Reviews, 9*. Accessed August 9, 2014, from http://almenpraksis.ku.dk/nyheder/oleolsen/Hjemmef_dsel.pdf

National Institute for Clinical Excellence (2014). *Intrapartum care: care of healthy women and their babies during childbirth. Clinical Guideline 190,* December 2014*.* Accessed December 15, 2014, from https://www.nice.org.uk/guidance/cg190/resources/guidance-intrapartum-care-care-of-healthy-women-and-their-babies-during-childbirth-pdf

Initial search – additional sources

Cochrane, A. L. (2000). 1931-1971: A critical review, with particular reference to the medical profession. *Medicines for the year*, 1-11.

College of Midwives of British Columbia. (2014). *Indications for discussion, consultation, and transfer of care*. Accessed August 4, 2014, from http://www.cmbc.bc.ca/pdf.shtml?Registrants-Handbook-12-01-Indications-for-Discussion-Consultation-and-Transfer-of-Care

College of Midwives of Ontario (2015). C*onsultation and transfer of care*. Accessed October 1, 2014, from http://www.cmo.on.ca/?page_id=1026

de Jonge, A., van der Goes, B. Y., Ravelli, A. C., Amelink-Verburg, M. P., Mol, B. W., Nijhuis, J. G., et al. (2009). Perinatal mortality and morbidity in a nationwide cohort of 529, 688 low-risk planned home and hospital births. *BJOG: An International Journal of Obstetrics & Gynaecology, 116*(9), 1177-1184.

Dowswell, T., Thornton, J. G., Hewison, J., Lilford, R. J., Raisler, J., MacFarlane, A., et al. (1996). Should there be a trial of home versus hospital delivery in the United Kingdom? *BMJ: British Medical Journal, 312*(7033), 753.

Hendrix, M., Van Horck, M., Moreta, D., Nieman, F., Nieuwenhuijze, M., Severens, J., et al. (2009). Why women do not accept randomisation for place of birth: feasibility of a RCT in the Netherlands. *BJOG: An International Journal of Obstetrics & Gynaecology, 116*(4), 537-544.

Hodnett E.D., Stremler R., Weston J.A., & Mckeever P. Reconceptualizing the hospital labor room: the Place (Pregnant and Laboring in an Ambient Clinical Environment) pilot trial. (2009). *Birth, 36*(2), 159–66.

Hutton, E. K., Reitsma, A. H., & Kaufman, K. (2009). Outcomes associated with planned home and planned hospital births in low-risk women attended by midwives in Ontario, Canada, 2003–2006: a retrospective cohort study. *Birth, 36*(3), 180-189.

Janssen, P. A., Saxell, L., Page, L. A., Klein, M. C., Liston, R. M., & Lee, S. K. (2009). Outcomes of planned home birth with registered midwife versus planned hospital birth with midwife or physician. *Canadian Medical Association Journal, 181*(6-7), 377-383.

Netherlands Ministry of Health, Welfare, and Sport. (n.d). *Final report of the obstetric working group of the national health insurance board of the Netherlands (abridged version)*. The Hauge, NL: Government of the Netherlands. Accessed August 4, 2014, from http://blog.lib.umn.edu/kuli0015/studygroup/Dutch%20OB%20Indications.doc

Oregon Health Authority. (2013). *Oregon birth outcomes by planned birth place and attendant*. Accessed August 1, 2014, from https://public.health.oregon.gov/BirthDeathCertificates/VitalStatistics/birth/Documents/PlannedBirthPlaceandAttendant.pdf

Wax, J. R., Lucas, F. L., Lamont, M., Pinette, M. G., Cartin, A., & Blackstone, J. (2010). Maternal and newborn outcomes in planned home birth vs planned hospital births: a meta-analysis. *American journal of obstetrics and gynecology, 203*(3), 243-e1.

Zeitlin, J., Mohangoo, A., Alexander, S., Barros, H., Blondel, B., Bouvier-Colle, et al. (n.d). *Health and care of pregnant women and babies in Europe in 2010*. Accessed on August 1, 2014 from http://www.europeristat.com/images/doc/Peristat%202013%20V2.pdf

The summary of these evidence sources in thie initial evidence summary for this document is derived directly from this evidence source, and portions are extracted verbatim.

New search (requested by EbGS at April 2, 2015 meeting) – included studies

Birthplace in England Collaborative Group; Brocklehurst, P., Hardy, P., Hollowell, J., Linsell, L., Macfarlane, A., McCourt, C. … Stewart, M. (2011). Perinatal and maternal outcomes by planned place of birth for healthy women with low risk pregnancies: The Birthplace in England national prospective cohort study. *British Medical Journal, 343*, d7400. http://www.bmj.com/content/343/bmj.d7400.full.pdf+html

Catling-Paull, C., Coddington, R. L., Foureur, M. J., Homer, C. S.; Birthplace in Australia Study; National Publically-funded Homebirth Consortium. (2013). Publically funded homebirth in Australia: A review of maternal and neonatal outcomes over 6 years. *Medical Journal of Australia, 198*(11), 616-20. https://www.mja.com.au/system/files/issues/198_11_170613/cat11665_fm.pdf

Cheng, Y. W., Snowden, J. M., King, T. L., & Caughey, A. B. (2013). Selected perinatal outcomes associated with planned home births in the United States. *American Journal of Obstetrics & Gynecology, 209*(4), 325.e1-8. http://www.ajog.org/article/S0002-9378(13)00630-3/pdf

Cheyney, M., Bovbjerg, M., Everson, C., Gordon, W., Hannibal , D., & Verdam, S. (2014). Outcomes of care for 16,924 planned home births in the United States: the Midwives Alliance of North

America Statistics Project, 2004-2009. *Journal of Midwifery & Women's Health, 59*(1), 17-27. http://onlinelibrary.wiley.com/doi/10.1111/jmwh.12172/epdf

Davis, D., Baddock, S., Paiman, S., Hunter, M., Benn, C., Anderson, J. … Herbison, P. (2012). Risk of severe postpartum hemorrhage in low-risk childbearing women in New Zealand: Exploring the effect of place of birth and comparing third stage management of labor. *Birth, 39*(2), 98-105. DOI: 10.1111/j.1523-536X.2012.00531.x

Janssen, P. A., Saxell, L., Page, L. A., Klein, M. C., Liston, R. M., & Lee, S. K. (2009). Outcomes of planned home birth with registered midwife versus planned hospital birth with midwife for physician. *Canadian Medical Association Journal, 181*(6-7), 377-83. http://www.cmaj.ca/content/181/6-7/377.full.pdf+html

de Jonge, A., Geerts, C. C., van der Goes, B. Y., Mol, B. W., Buitendijk, S. E., & Nijuhuis, J. G. (2015). Perinatal mortality and morbidity up to 28 days after birth among 743,070 low-risk planned home and hospital births: A cohort study based on three merged national perinatal databases. *British Journal of Obstetrics and Gynecology, 122*(5), 720-728. http://onlinelibrary.wiley.com/doi/10.1111/1471-0528.13084/epdf

de Jonge, A., Mesman, J. A., Mannien, J., Zwart, J. J., van Dillen, J., & van Roosmalen, J. (2013). Severe adverse maternal outcomes among low risk women with planned home versus hospital births in the Netherlands: Nationwide cohort study. *British Medical Journal, 346*, f3263. http://www.bmj.com/content/346/bmj.f3263.full.pdf+html

de Jonge, A., van der Goes, B. Y., Ravelli, A. C., Amelink-Verburg, M. P., Bol, B. W., Nijhuis, J. G. … Buitendijk, S. E. (2009). Perinatal mortality and morbidity in a nationwide cohort of 529,688 low-risk planned home and hospital births. *British Journal of Obstetrics and Gynecology, 116*(9), 1177-84. http://onlinelibrary.wiley.com/doi/10.1111/j.1471-0528.2009.02175.x/epdf

Hutton, E. K., Reitsma, A. H., & Kaufman, K. (2009). Outcomes associated with planned home and hospital births in low-risk women attended by midwives in Ontario, CA, 2003-2006: A retrospective cohort study. *Birth, 36*(3), 180-9. http://www.aom.on.ca/files/Communications/Reports_and_Studies/Birth_Ontario_Home_Birth_Hutton_Sept_09.pdf

Johnson, K. C., & Daviss, B. A. (2005). Outcomes of planned home births with certified professional midwives: Large prospective study in North America. *British Medical Journal, 330*(7505), 1416. http://www.bmj.com/content/330/7505/1416.full.pdf+html

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Nove, A., Berrington, A., & Matthews, Z. (2012). Comparing the odds of postpartum haemorrhage in planned home birth against planned hospital birth: Results of an observational study of over 500,000 maternities in the UK. *BMC Pregnancy & Childbirth, 12*, 130. http://www.biomedcentral.com/content/pdf/1471-2393-12-130.pdf

Stapleton, S. R., Osborne, C., & Illuzzi, J. (2013). Outcomes of care in birth centers: Demonstration of a durable model. *Journal of Midwifery & Women's Health, 58*(1), 3-14. http://onlinelibrary.wiley.com/doi/10.1111/jmwh.12003/epdf

van der Kooy, J., Poeran, J., de Graaf, J. P., Bimie, E., Denklass, S., Steegers, E. A., & Bonsel, G. J. (2011). Planned home compared with planned hospital births in the Netherlands: Intrapartum and early neonatal death in low-risk pregnancies. *Obstetrics & Gynecology, 118*(5), 1037-46. DOI: 10.1097/AOG.0b013e3182319737

TOPIC BACKGROUND

The Licensed Direct Entry Midwife (LDM) Staff Advisory Workgroup was convened in January 2014 by the Director of the Oregon Health Authority (OHA). The workgroup was established to provide recommendations regarding perinatal services provided to Medicaid enrollees by LDMs. The workgroup was guided by the Triple Aim goals of improving population health, improving the individual's experience of care, and reducing per capita costs. One of the recommendations of the final report of this workgroup to the OHA was to request that the Health Evidence Review Commission develop a Coverage Guidance related to home birth, including evidence regarding:

- The maternal and fetal/neonatal/child health outcomes of home birth compared with birth in other settings
- Appropriate candidates for home birth
- Criteria for optimizing safety with regard to provider training, equipment, standards, consultation, and other systems of care

EVIDENCE OVERVIEW

Clinical background

From Cochrane 2012

Medicalization of childbirth is a central feature in Western societies. The majority of women living in high and middle-income countries have given birth in hospitals since the middle of the 20th century. However, there are regions where home birth is considered part of normal practice. The most cited case is the Netherlands where planned home birth is supported by the official healthcare system. There, planned home birth is considered an appropriate choice for a woman of low risk and approximately 30% of all births take place at home. It is of historical interest to note that the transfer of low-risk births from home to hospital in the 1960s, despite lack of high-quality evidence, was one of the pivotal issues when Archie Cochrane laid out the ideological ground for The Cochrane Collaboration. Cochrane awarded 'the wooden spoon' to obstetrics, because "the specialty missed its first opportunity in the sixties, when it failed to randomize the confinement of low-risk pregnant women at home or hospital. Then, having filled the emptying beds by getting nearly all pregnant women into hospital, the obstetricians started to introduce a whole series of expensive innovations into the routines of pre- and postnatal care and delivery, without any rigorous evaluation. The list is long, but the most important were induction, ultrasound, fetal monitoring, and placental function tests" (Cochrane 1979). The relationship between hospitalization, childbirth, and intervention is still an important issue as "Concern about the iatrogenic

effects of obstetric intervention in women who do not have a clinical need for it has put 'normal' birth firmly on the agenda for the 21st century." (EURO-PERISTAT 2008).

A range of interventions continue to be used routinely in relation to births at many hospitals despite the fact that for a long time they have been proven to have harmful effects, or only marginal or no beneficial effect (e.g., fetal monitoring, episiotomy and early cord clamping). Even though the use of a few specific interventions have been reduced (e.g., placental function tests), in general "routine medical interventions have [...] increased steadily over time despite the efforts of the Cochrane Pregnancy and Childbirth Group, its predecessors, and other researchers carrying out systematic reviews" (Hodnett 2009).

The Cochrane review is about healthy pregnant women at term for whom no serious complications have been identified prior to the spontaneous initiation of birth and for which the birth is expected to be medically uncomplicated. Generally, between 70% and 80% of all pregnant women may be considered as low risk at the start of labor.

Initial evidence review

Cochrane 2012

The inclusion criteria for the Cochrane 2012 review was limited to randomized controlled trials that compared planned hospital births to planned home births. Authors identified two RCTs; however one was only able to recruit one patient. This study (Hendrix 2009) was conducted in the Netherlands and recruited nulliparous women of low obstetric risk (n = 1). In this trial, 35 midwives in 14 primary care midwifery practices were involved in recruiting pregnant women in different parts of the Netherlands where 30% of all births are home births. However, the study author reported that only one of 116 women was willing to be randomized, the others having all decided where they wanted to deliver before being recruited into the study.

The second trial, Dowswell 1996, was conducted in the United Kingdom and recruited multiparous women judged to be at low obstetric risk by a consultant obstetrician and likely to have suitable home support and home circumstances (n = 71). Recruitment was carried out by one consultant obstetrician in an area where planned home birth was otherwise uncommon (0.5% to 1%). The midwives assisting the home births were community midwives who spent a few days each month in hospital; all UK midwives are trained to do home births, but the ones in the trial were probably not experienced with home birth. The hospital births were standard hospital care with intermittent auscultation at a university hospital with consultant obstetrician on call (but not called routinely) and full neonatal facilities. One midwife served one to two women in single rooms; she used intermittent auscultation and was not continuously present. This study was rated as having high methodologic quality, except for the small size.

The fully assessed trial with reported outcomes was too small to draw reliable conclusions. Only 11 women agreed to randomization. Four of the primary outcomes in this review were available for inclusion: baby not breast fed, assisted vaginal birth, caesarean section, and other (non-epidural) medical pain relief. In addition, three other outcomes were reported and these are also included here: perineal sutures, mother disappointed about allocation, and father did not state that he was relieved. One difference seems statistically significant: the majority of mothers in the hospital group were disappointed about the allocation while none of the mothers in the home birth group were disappointed

[(Peto odds ratio 12.18, 95% confidence interval (CI) 1.05 to 141.17; however, the difference is non-significant using a Fisher's exact test P value = 0.07)]. There were no instances of assisted vaginal birth or cesarean section, and for the other outcomes, there were no statistically significant differences between groups.

The Cochrane authors report that these results do not "contradict the evidence from the largest observational studies (de Jonge 2009; Hutton 2009; Janssen 2009) identified in the most recent systematic review (Wax 2010)."

Because of the paucity of RCTs addressing this comparison, the systematic review and observational studies listed above are summarized below.

Wax 2010

This systematic review did not limit inclusion criteria by study design. The search was through November 2009, and included MEDLINE, EMBASE and Cochrane Database of Systematic Reviews. Inclusion criteria included performance in developed western countries, English language, peer reviewed and outcomes analyzed by planned delivery location. Twelve studies were included, including the three cohort studies described below and the single RCT described above, with a total of 342,056 planned home and 207,551 planned hospital deliveries.

Meta-analysis of maternal outcomes found that planned home births experienced significantly fewer medical interventions including epidural analgesia, electronic fetal heart rate monitoring, episiotomy, and operative vaginal and cesarean deliveries. Likewise, women intending home deliveries had fewer infections, third degree lacerations, perineal and vaginal lacerations, hemorrhages, and retained placentas. There was no significant difference in the rate of umbilical cord prolapse.

Meta-analysis of neonatal outcomes found that women planning home births were less likely to have preterm deliveries or babies who were low birth weight. Planned home births more often progressed to at least 42 weeks. While there was no overall pooled difference in the rate of assisted ventilation, one large study found more frequent ventilation among planned home births, while two smaller studies noted lower rates in this group. Perinatal mortality was similar by intended delivery location (OR 0.95 95% CI 0.77 to 1.18), as well as just among non-anomalous offspring (OR 0.95, 95% CI 0.76 to 1.18). In contrast, neonatal mortality was almost twice as high in planned home versus planned hospital births (OR 1.98, 95% CI 1.19 to 3.28, absolute number 32 out of 16,500 planned home births [0.20%] compared to 32 out of 33,302 planned hospital births [0.09%]), and almost tripled among non-anomalous neonates (OR 2.87, 95% CI 1.32 to 6.25, absolute number 23 out of 15,633 planned home births [0.15%] compared to 14 out of 31,999 planned hospital births [0.04%]). While the reason for the difference between neonatal and perinatal mortality rates is unclear from this analysis, the authors speculate that it may be due to the lower obstetric risk associated with patients planning home births. If this is the case, planned home births may face a higher perinatal mortality rate than similar risk planned hospital births.

The results of the sensitivity analyses excluding studies that included home births attended by other than certified midwives or certified nurse midwives had findings similar to the original analysis, except that the ORs for neonatal deaths among all (OR, 1.57; 95% CI, 0.62–3.98) and non-anomalous (OR, 3.00; 95% CI, 0.61–14.88) newborns were not statistically significant.

de Jonge 2009

This is a nationwide cohort study conducted in the Netherlands that included a total of 529,688 low-risk women who were in primary midwife-led care at the onset of labor. In the Netherlands, the indications for referral to an obstetrician have been agreed upon by the professional groups involved and are laid out in the "Obstetric Indication List" (see Appendix A). Of these, 321,307 (60.7%) intended to give birth at home, 163,261 (30.8%) planned to give birth in hospital and for 45,120 (8.5%), the intended place of birth was unknown. Authors adjusted for a number of maternal characteristics (e.g., parity, gestational age, maternal age, ethnic background and socioeconomic status).

No significant differences were found between planned home and planned hospital birth in neonatal outcomes reported. Adjusted relative risks (RR) and 95% CI were as follows: intrapartum death (RR 0.97, 95% CI: 0.69 to 1.37), intrapartum death and neonatal death during the first 24 hours (RR 1.02, 95% CI: 0.77 to 1.36), intrapartum death and neonatal death up to 7 days (RR 1.00, 95% CI: 0.78 to 1.27), admission to neonatal intensive care unit (RR 1.00, 95% CI: 0.86 to 1.16).

Hutton 2009

Midwives in Ontario, Canada, provide care in the home and hospital and are required to submit data for all births to the Ontario Ministry of Health database. The purpose of this study was to compare maternal and perinatal/neonatal mortality and morbidity and intrapartum intervention rates for women attended by Ontario midwives who planned a home birth compared with similar low-risk women who planned a hospital birth between 2003 and 2006. The following types of pregnancies are not eligible for home birth in Ontario:

- Twins
- Breech
- Medical complications in the mother
- More than one prior cesarean section
- Gestational age less than 37 or more than 42 weeks

The database provided outcomes for all women planning a home birth at the onset of labor (n = 6,692) and for a cohort, stratified by parity, of similar low-risk women planning a hospital birth. The rate of perinatal and neonatal mortality was very low (1/1,000) for both groups, and no difference was shown between groups in a composite measure of perinatal and neonatal mortality or serious morbidity (RR 2.4% vs 2.8%, 95% CI: 0.84 [0.68–1.03]). No maternal deaths were reported. All measures of maternal morbidity were lower in the planned home birth group, including augmentation (RR 0.76, 95% CI 0.72 to 0.80), pharmaceutical pain relief (RR 0.37, 95% CI 0.35 to 0.39), episiotomy (RR 0.73, 95% CI 0.63 to 0.84), assisted delivery (RR 0.67, 95% CI 0.56 to 0.80), perineal trauma (RR 0.87, 95% CI 0.83 to 0.90), and blood loss greater than 1,000 ml (RR 0.68, 95% CI 0.49 to 0.96). In addition, the rates for cesarean section were lower in the planned home birth group (5.2% vs 8.1%, RR 0.64, 95% CI 0.56 to 0.73). When stratified by parity, nulliparas were less likely to deliver at home, and had higher rates of ambulance transport from home to hospital than multiparas planning home birth. However, nulliparas planning home birth still had rates of intervention and outcomes that were similar to, or lower than, nulliparas planning hospital births.

Janssen 2009

This study was also a retrospective cohort study utilizing a database of all births in the province of British Columbia that occurred between 2000 and 2004. Eligibility for home birth by the College of Midwives of British Columbia includes the following:

- Absence of significant pre-existing disease in the mother
- Absence of significant disease arising during pregnancy (e.g., pregnancy-induced hypertension, hemorrhage, diabetes, herpes, placenta previa, abruption)
- Singleton fetus
- Cephalic presentation
- Gestational age between 36 and 41 weeks
- No more than one prior cesarean section
- Spontaneous labor (or induced as an outpatient)
- No transfer from a referring hospital

Planned home births were compared to midwife attended planned hospital births and physician attended planned hospital births, both limited to patients who met the criteria for home birth and matched by age, parity, single parent status, maternal age, and hospital location. There were 2,899 women in the planned home birth group, 4,752 in the planned hospital birth group attended by midwives, and 5,331 in the planned hospital group attended by physicians.

The perinatal mortality rate was 0.35/1,000 births in the home birth group, 0.57/1,000 in the hospital midwife group and 0.64/1,000 in the hospital physician group, with no statistically significant differences between groups (RR for home midwife vs. hospital midwife 0.61, 95% CI 0.06 to 5.88; RR for home midwife vs. hospital physician 0.55, 95% CI 0.06 to 5.25). Infants in the planned home birth group were significantly less likely to have an Apgar score less than seven at one minute, to suffer birth trauma, or to require resuscitation or oxygen therapy for more than 24 hours when compared to either hospital group.

Compared to planned home birth, the frequency of obstetric interventions was higher in the planned hospital group (either physician or midwife), including fetal monitoring (RR 0.32, 95% CI 0.29 to 0.36 for midwife, RR 0.17, 95% CI 0.16 to 0.19 for physician), augmentation of labor (RR 0.59, 95% CI 0.55 to 0.69 for midwife, RR 0.47, 95% CI 0.44 to 0.51 for physician), assisted vaginal delivery (RR 0.41, 95% CI 0.33 to 0.52 for midwife, RR 0.22, 95% CI 0.18 to 0.27 for physician), cesarean section (RR 0.76, 95% CI 0.64 to 0.91 for midwife, RR 0.65, 95% CI 0.56 to 0.76 for physician) and episiotomy (RR 0.49, 95% CI 0.38 to 0.63 for midwife, RR 0.19, 95% CI 0.15 to 0.23 for physician). They were also more likely to have third or fourth degree perineal tears (RR 0.43, 95% CI 0.29 to 0.63 for midwife, RR 0.34, 95% CI 0.24 to 0.49 for physician).

April 2015 New Evidence Search Results

(References listed on pages six to nine.)

Background

At the April 2, 2015 meeting, the EbGS asked for a full evidence search on OOH birth literature due to concerns raised in public comment and testimony about the completeness of evidence identified in the initial trusted source search published to the OHA website in August 2014. Public comments and testimony raised the issue of risk of perinatal mortality, particularly for primiparous women, in planned OOH birth. It also raised the issue of assuring that the evidence spoke to planned OOH birth compared to planned hospital birth, with the recognition that unplanned OOH birth was outside the topical area and that mixing evidence from these two populations would be misleading. Staff were also concerned that the initial search did not explicitly include birth centers. Amending the coverage guidance to encompass this site, staff determined that a broader, new evidence search was warranted. The new evidence search focused on perinatal mortality and mode of birth because those outcomes appeared to encompass both the greatest potential harm and benefit of OOH birth. In addition, the new search explicitly included terms related to birth centers since the initial search was focused on home birth. Appendix C includes details about the search, inclusion criteria, review methodology, and a full evidence table with the 15 included studies.

New Evidence Search

The new evidence search (MEDLINE®) conducted on April 22, 2015 yielded 596 citations and a final search on May 20, 2015 identified an additional 21 citations. The MEDLINE® search was limited to the past 10 years and not limited by study design.These 617 citations were subject to dual review for possible inclusion. See Appendix C for details on the search strategy and inclusion criteria. Inclusion criteria specified study size, relevant fetal/neonatal and maternal outcomes, and location of study. At least one study arm had to include subjects with planned OOH birth, either at home or in a birth center. Two staff epidemiologists reviewed 40 full text articles and found 15 that met inclusion criteria. All included studies were dual rated for quality of evidence for key oucomes, based on the GRADE system. No study was excluded based on quality in accord with accepted practice for systematic reviews (SRs). See Appendix C for GRADE quality ratings.

The new search located two SRs and no randomized controlled trials (RCTs). The first SR (Olsen, 2012) was the Cochrane Review discussed in the prior evidence summary. It included two RCTs, one with a single patient and another with 11 subjects. Neither of these individual trials met the new evidence search inclusion criteria based on study date and sample size. The second SR identified (Wax, 2010) was also identified in the trusted sources and is discussed in the initial evidence summary above. It was excluded from the new evidence summary because, on closer examination, it was clear that it incorporated studies including women who had unplanned births at home rather than restricting inclusion to studies reporting planned home birth exclusively. Three of 12 studies included in the Wax (2010) SR are also included in this new evidence search and summary. Nine of 12 of the individual studies captured in the Wax SR (2010) were excluded from the new evidence search on the basis of date (published more than 10 years ago). It appears that the new search strategy was more comprehensive than that used by Wax (2010), yielding 617 citations as compared with 237 for Wax (2010). The 15 studies meeting final inclusion criteria are included in the evidence table in Appendix C.

Results

Context

To contextualize the results it is important to understand baseline risks of perinatal mortality and other harms among women experiencing hospital births. For the U.S. as a whole, perinatal mortality has remained relatively stable over recent years.[1] Perinatal mortality is defined and reported in the U.S. in two ways: first, as the number of fetal and early neonatal deaths (0 to 7 days of life) per 1000 live births and eligible fetal deaths (over 20 weeks of gestation); and second, with the addition of late neonatal deaths (those taking place between 7 and 28 days of life).[2] Some countries and studies use alternate definitions, such as reporting only neonatal deaths during the first week of life (early neonatal death) or only including gestations above 24 weeks, making international comparison difficult. However, there are still clear differences across countries and among populations, even with these definitional issues. For example, the World Health Organization reported a 2000 perinatal mortality rate of 6 in Australia, Belgium, Finland, and Canada; 7 for the U.S.; 8 for the U.K. and rising to rates well above 80 in many countries of the developing world.[3] The U.S. National Center for Health Statistics (NCHS) reported a U.S. rate (first definition, using stillbirths and early neonatal deaths) of 6.51 in 2006 with a slight decline to 6.26 in 2011,[1] but did not report perinatal mortality by parity. However, the risk of perinatal death varies by gestational age and co-existing maternal and fetal/neonatal factors. For example, infant mortality rates for low-risk pregnancies at term vary from a high of 0.66 at 37 weeks to a nadir of 0.33 at 39 weeks and an intermediate level of 0.40 at 41 weeks.[4] Similarly, the fetal mortality rate varies from 1.40 at 37 to 39 weeks, to 0.88 at 40 weeks and increases late in pregnancy to 1.76 at 42 or more weeks of gestation.[2]

In 2006, the overall perinatal mortality rate in Oregon was 5.27.[2] During 2012, there were 92 reported term fetal deaths and early neonatal deaths in the state. Of these 92 deaths, 84 occurred in planned hospital births and 8 occurred in planned OOH births.[5] These rates were not reported by parity. Chart review of the eight cases of intrapartum and early neonatal death found that six of the eight did not meet low-risk criteria. The total term perinatal mortality rate for planned OOH births in Oregon in 2012 was 4.0 and for planned in-hospital births was 2.1.[5]

The perinatal mortality rate, and perinatal morbidity more generally, is higher among women having a first birth (primiparous women) than those having a subsequent birth (multiparous women), regardless

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[1] Gregory, E.C., MacDorman, M.F., & Martin, J.A. (2014). Trends in fetal and perinatal mortality in the United States, 2006-2012. *NCHS Data Brief*, Nov(169), 1-8. http://www.cdc.gov/nchs/data/databriefs/db169.pdf

[2] MacDorman, M. F., Kirmeyer, & S. E., Wilson, E.C. (2012). Fetal and perinatal mortality. United States, 2006. *National vital statistics reports, 60*(8). http://www.cdc.gov/nchs/data/nvsr/nvsr60/nvsr60_08.pdf

[3] World Health Organization (WHO). (2006). Neonatal and Perinatal Mortality. Country, Regional and Global Estimates. Geneva: WHO Press. http://whqlibdoc.who.int/publications/2006/9241563206_eng.pdf

[4] Zhang X., & Kramer, M. S. (2009). Variations in mortality and morbidity by gestational age among infants born at term. *Journal of Pediatratrics, 154*(3), 358-62. DOI: http://dx.doi.org/10.1016/j.jpeds.2008.09.013

[5] Oregon Public Health Division. (2013). Oregon Birth Outcomes, by Planned Birth Place and Attendant. Persuant to: HB 2380. Prepared by Oregon Public Health Division, August 30, 2013. Available at: http://public.health.oregon.gov/BirthDeathCertificates/VitalStatistics/birth/Documents/PlannedBirthPlaceandAttendant.pdf

of birth setting. For example, Cheng (2013) found that the risk of low Apgar score was nearly twice as high among low risk primiparous women having a hospital birth in the U.S. than among multiparous women in that setting. The Birthplace study, conducted in the U.K., reported that the incidence of stillbirth among low risk multiparous women giving birth in hospital obstetric units was half of what it was for primiparous women in the same types of hospital settings (Birthplace, 2011). They also reported that the incidence of neonatal death within the first week of life was four times as common among primiparas (Birthplace, 2011). Similarly, de Jonge (2009) reported that the adjusted relative risk of stillbirth or death within the first week of life was 1.68 for primiparous women compared to multiparous women in a study from the Netherlands. While the absolute risk of these outcomes is low, it is important to note the relative baseline differences among first and subsequent births.

Summary of Results – New Search

A summary table of included studies and results for our primary outcomes of interest is presented in Table 1 below. Four of the 15 studies were conducted in the U.S. and the remainder were based in Australia, Canada, England, the Netherlands, and New Zealand. Two studies provided low quality evidence for the primary outcomes of interest and 13 studies yielded very low quality evidence. This is largely because all studies were observational and most (11 of 15) were conducted outside the U.S., thus introducing indirectness and potential for non-comparability to the U.S. setting. Ten studies reported measures of perinatal mortality with definitions ranging from intrapartum fetal deaths plus neonatal deaths within the first 24 hours of life up to 28 days. These rates (per 1000 births) ranged from 0.87 to 2.06 for planned home birth among non-comparative studies. Among comparative studies, perinatal mortality (measured as stillbirths and neonatal deaths up to 28 days) ranged from a protective relative risk (RR) of 0.61 in the Canadian study by Janssen (2009) to an excess adjusted RR of 1.38 in the Australian study by Kennere (2009). No confidence interval (CI) was statistically significant and the CIs of these studies were overlapping. Cesarean delivery rates were low overall, but statistically lower in the planned OOH birth group among comparative studies. Two studies contributed data only on postpartum hemorrhage (Davis, 2011; Nove, 2012). Both found a decreased risk of postpartum hemorrhage with home birth, but only one of these findings was statistically significant.

Table 1. Summary of Included Studies from New Search, Primary Outcomes of Interest Reported, and Study Quality

Citation	Study Description • Country • Study design • Number of planned OOH births included	Primary Fetal & Neonatal Outcome Reported	Primary Maternal Outcome Reported	Study Quality (GRADE)
Birthplace, 2011	• England • Prospective comparative cohort comparing planned home (n=16,840),	Composite outcome (CO) (stillbirth, neonatal death 0-7d, neonatal encephalopathy, meconium aspiration, brachial plexus	Cesarean delivery Cesarean incidence/1000 (99% CI), by site	Very low (OOO+)

Citation	Study Description • Country • Study design • Number of planned OOH births included	Primary Fetal & Neonatal Outcome Reported	Primary Maternal Outcome Reported	Study Quality (GRADE)
	freestanding midwifery unit (FMU) (11,282), alongside midwifery unit (AMU) (n=16,710), and obstetric unit (OU) (n=19,706) sites	injury, fractured humerus or clavicle) CO incidence (95% CI), by site Home 4.2 (3.2-5.4) FMU 3.5 (2.5-4.9) AMU 3.6 (2.6-5.9) OU 4.4 (3.2-5.9)	Home 2.8 (2.3-3.4) FMU 3.5 (2.8-4.2) AMU 4.4 (3.5-5.5) OU 11.1 (9.5-13.0)	
Catling-Paull, 2013	• Australia • Retrospective, non-comparative cohort of planned home birth • 1807	Perinatal mortality (fetal to 7d) Home 1.7/1000	Cesarean delivery Home 5.4%	Very low (OOO+)
Cheng, 2013	• U.S. • Retrospective cohort comparing planned home birth to hospital birth using vital statistics data (27 states) • 12,039	5 minute Apgar score < 4 Home v. Hospital adjOR 1.87 (95% CI 1.36-2.58)	Operative vaginal delivery Home v. Hospital adjOR 0.12 (95% CI 0.08-0.17)	Very low (OOO+)
Cheyney, 2014	• U.S. • Prospective, non-comparative cohort of planned home birth • 16,924	Perinatal mortality (intrapartum to 28d) Home (non-anomalous) 2.06/1000	Cesarean delivery Home 5.2%	Low (OO++)
Davis, 2011	• New Zealand • Retrospective, comparative cohort of planned home birth and planned hospital (primary, secondary, tertiary) birth	*None*	Postpartum hemorrhage (>1000mL) Home v.Primary hospital adjOR 0.93	Very low (OOO+)

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Citation	Study Description • Country • Study design • Number of planned OOH births included	Primary Fetal & Neonatal Outcome Reported	Primary Maternal Outcome Reported	Study Quality (GRADE)
	• 1830		(95% CI 0.49-1.74)	
de Jonge, 2009	• Netherlands • Retrospective cohort study of planned home and planned hospital birth • 466,041	Perinatal mortality (intraparum to 7d) Home v. Hospital adjRR 1.00 (95%CI 0.78-1.27)	*None*	Very low (OOO+)
de Jonge, 2013	• Netherlands • Retrospective cohort study of planned home and planned hospital birth • 92,333	*None*	Composite outcome (ICU admission, uterine rupture, eclampsia/preeclampsia, transfusion) incidence Home v. Hospital 1.5/1000 v. 2.7/1000	Very low (OOO+)
de Jonge, 2015	• Netherlands • Retrospective cohort study of planned home and planned hospital birth • 335,683	Perinatal mortality (intrapartum to 28d) Home v. Hospital (nulliparous) adjOR 0.99 (95% CI 0.79-1.24) Home v. Hospital (multiparous) adjOR 1.16 (95% CI 0.87-1.55)	*None*	Very low (OOO+)
Hutton, 2009	• Ontario, Canada • Retrospective matched cohort of planned home birth • 6692	Perinatal mortality (intrapartum to 28d) Home v. Hospital 9/6692 (0.13%) v. 8/6692	Cesarean delivery Home v. Hospital RR 0.64	Very low (OOO+)

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Citation	Study Description • Country • Study design • Number of planned OOH births included	Primary Fetal & Neonatal Outcome Reported	Primary Maternal Outcome Reported	Study Quality (GRADE)
		(0.12%)	(95% CI 0.56-0.73)	
Janssen, 2009	• British Columbia, Canada • Retrospective cohort of planned home and planned hospital births • 2889	Perinatal mortality (intrapartum to 28d) Home v. Hospital (both with registered midwife) RR 0.61 (95% CI 0.06-5.88)	Cesarean delivery Home v. Hospital (both with registered midwife) adjRR 0.76 (95% CI 0.64-0.91)	Very low (OOO+)
Johnson, 2005	• U.S. • Retrospective, non-comparative cohort of planned home births • 5418	Perinatal mortality (intrapartum to neonatal) Home (non-anomalous) 2.03/1000	Cesarean delivery Home 3.7%	Very low (OOO+)
Kennere, 2009	• South Australia • Retrospective cohort of planned home and planned hospital births • 1141	Perinatal mortality (intrapartum to 28d) Home v. Hospital adjOR 1.38 (95% CI 0.56-3.41)	Cesarean delivery Home v. Hospital adjOR 0.27 (95% CI 0.22-0.34)	Very low (OOO+)
Nove, 2012	• North West Thames Region, England • Retrospective cohort of planned home and planned hospital births • 5598	*None*	Postpartum Hemorrhage (>1000mL) Home v. Hospital adjOR 0.40 (95% CI 0.26-0.59)	Very low (OOO+)
Stapleton, 2013	• US • Retrospective, non-comparative cohort of planned birth center birth • 15, 574	Perinatal mortality (intrapatum to 7d) Birth center (non-anomalous) 0.87/1000	Cesarean delivery Home 6.1%	Low (OO++)
van der	• Netherlands	Perinatal mortality	*None*	Very low

Citation	Study Description • Country • Study design • Number of planned OOH births included	Primary Fetal & Neonatal Outcome Reported	Primary Maternal Outcome Reported	Study Quality (GRADE)
Kooy, 2011	• Retrospective cohort of planned home and planned hospital births • 402,912	(intrapartum to 7d) Home v. Hospital adjRR 1.05 (95% CI 0.91-1.21)		(OOO+)

Table Abbreviations: adjOR – adjusted odds ratio; AMU – planned alongside midwifery unit birth; CI – confidence interval; CO – composite outcome; d – days; FMU – planned freestanding midwifery unit birth; home – planned home birth; n – number of subjects in study or group; OOH – out of Hospital; OU – planned obstetric unit birth; RR – relative risk.

Note: Study quality: (OOO+) represents very low, (OO++) represents low.

While several studies presented data on the overall perinatal mortality rate for the entire study population of women having a first birth and women having subsequent birth, only four studies provided those data by parity. See Table 2 below for perinatal mortality outcomes reported by parity. Only one non-comparative U.S.-based study contributed information on the risk of perinatal mortality among primiparous women compared to multiparous women. Cheyney (2014) reported 18/3771 (0.48%) cases of perinatal death (intrapartum stillbirth through 28 days) among primiparas compared to 17/13,153 (0.13%) for multiparas. The unadjusted intrapartum stillbirth rate was 2.92 vs. 0.84 for primiparas compared to multiparas. Among primiparous women experiencing perinatal death, eight women had risk factors including breech presentation, gestational diabetes and preeclampsia. For the 10 cases of perinatal death among women who did not have these risk factors, the intrapartum stillbirth rate was 2.21; the early neonatal perinatal mortality rate was 0.28; and the late neonatal mortality rate was also 0.28, for a total perinatal mortality rate of 2.77 among low-risk primiparous women (Cheyney, personal communication, 2015).

Table 2. Perinatal Mortality, New Search, Among Studies Reporting by Parity

Citation, Year (Country) [Quality]	Perinatal Mortality (PM) – Primiparous Women (per 1000 births)	Perinatal Mortality (PM) – Multiparous Women (per 1000 births)	Total Deaths Reported (total N of study)
Cheyney, 2014 (U.S.) [OO++]	Crude PM (Home) Intrapartum: 2.92 Early neonatal: 0.41 Late neonatal: 0.80 Total crude PM, primiparas: 4.13	Crude PM (Home) Intrapartum: 0.84 Early neonatal: 0.27 Late neonatal: 0.23 Total crude PM: 1.34	35 (N=16,924)

Citation, Year (Country) [Quality]	Perinatal Mortality (PM) – Primiparous Women (per 1000 births)	Perinatal Mortality (PM) – Multiparous Women (per 1000 births)	Total Deaths Reported (total N of study)
	adjPM (Home), parimiparas 2.77 (after excluding high risk)	(*adjPM not reported*)	
Birthplace, 2011 (England) [OOO+]	Intrapartum Stillbirth (n (95% CI) Home 0.9 (0.2-3.3) FMU 0.3 (0.0-3.5) AMU 0.1 (0.0-1.6) OU 0.1 (0.0-1.5) Early Neonatal Death (n (95% CI) Home 0.4 (0.1-2.4) FMU 0.5 (0.1-1.7) AMU 0.1 (0.0-1.7) OU 0.4 (0.1-1.3)	Intrapartum Stillbirth (n (95% CI) Home 0.1 (0.0-0.9) FMU 0.5 (0.1-2.2) AMU 0 events OU 0.2 (0.0-1.2) Early Neonatal Death (n (95% CI) Home 0.3 (0.1-1.3) FMU 0.3 (0.1-2.2) AMU 0.1 (0.0-1.4) OU 0.1 (0.0-1.8)	32 (N=44,434)
Hutton, 2009 (Canada) [OOO+]	PM (fetal death to neonatal 28d) Home: 2.18 Hospital: 1.74	PM (fetal death to neonatal 28d) Home: 0.91 Hospital: 0.91	18 (N=13,384)
de Jonge, 2015 (Netherlands) [OOO+]	PM (fetal death to neonatal 28d) Home: 1.02 Hospital: 1.09	PM (fetal death to neonatal 28d) Home: 0.59 Hospital: 0.58	592 (N=743,070)

Table Abbreviations: adj – adjusted; AMU – planned alongside midwifery unit birth; CI – confidence interval; d – days; FMU – planned freestanding midwifery unit birth; home – planned home birth; N – number of subjects in study; OU – planned obstetric unit birth; PM – perinatal mortality. -number of subjects in study.

Note: Study quality (OOO+) represents very low , (OO++) represents low.

U.S.-based Studies Reporting Perinatal Mortality and Cesarean Delivery Rate

There were four U.S.-based studies with two presenting low quality evidence (Cheyney, 2014; Stapleton, 2013) and two with very low quality evidence (Cheng, 2013; Johnson, 2005). Neither of the low quality evidence studies was comparative, but both were large and well-conducted (Cheyney, 2014; Stapleton, 2013). Cheyney (2014) presented data on home birth and the Stapleton (2013) studied birth center outcomes. Cheng (2013) did not report perinatal mortality and is discussed in a separate section below.

Johnson (2005) used data collected by midwives registered by the North American Registry of Midwives (NARM) as a requirement of recertification. It is smaller and older than Cheyney (2014), but similar in that it was conducted by a midwifery registration organization.

For home birth in the U.S., Cheyney (2014) found a non-anomalous perinatal mortality rate (stillbirth to neonatal death within 28 days) of 2.06. Johnson (2005) reported a similar finding with a non-anomolous perinatal mortality rate (intrapartum stillbirth to 28 days) of 2.03. Stapleton (2013) reported a non-anomalous perinatal mortality rate (stillbirth to neonatal death within 7 days) of 0.87. The reported cesarean delivery rates were similar across the U.S.-based studies, ranging from 3.7% (Johnson, 2005) to 5.2% (Cheyney, 2014) to 6.1% (Stapleton, 2013).

U.S.-based Study Reporting Low Apgar Score Outcome

The fourth U.S.-based study did not report perinatal mortality, but instead reported the surrogate outcome of low Apgar score (5-minute Apgar score less than 4) (Cheng, 2013). Cheng (2013) reported lower odds (but not statistically different) of low Apgar score for home births attended by certified nurse midwives (CNMs) compared to hospital births for either primiparous or multiparous women (adjusted odds ratio [adjOR] 0.47 [95% CI 0.55-3.22]; adjOR 0.83 [95% CI 0.27-2.60]). When the comparison was for home birth attended by other types of midwives compared with hospital birth, Cheng and colleagues (2013) found the odds of low Apgar score to be elevated in both parity groups (not statistically significant for primiparous women, but statistically significant for multiparous women), with the adjOR of 1.34 (95%CI 0.55-3.22) for primiparas and an adjOR of 1.84 (95% CI 1.04-3.26) for multiparas. Based on other research, the association between a low 5-minute Apgar and the live born infant dying when this occurs is moderate, with about 20 neonatal deaths out of every 1000 (2%) births.[6,7] Other methodologic limitations also exist for this type of birth certificate-based study[8,9] and contributed to the rating of very low quality evidence for this study.

Non-U.S.-based Studies Reporting Perinatal Mortlity by Parity

Among non-U.S. studies, three provided information on perinatal mortality by parity and compared planned home and hospital birth (Birthplace, 2011; de Jonge, 2015; Hutton, 2009). The information from the prospective Birthplace study (2011) for stillbirth and neonatal death in the first week of life should be interpreted cautiously as these items were not the primary outcome (which was a composite outcome including both items, but also including items such as humeral and clavicular fracture). Total event rates were small, confidence intervals (CI) are wide, and only unadjusted figures are available from the online appendices to the article. For primiparous women, the rate of stillbirth with planned

[6] Casey, B. M., McIntire, D. D., & Leveno, K. J. (2001). The continuing value of the Apgar score for the assessment of newborn infants. *New England Journal of Medicine, 344*(7), 467-471.

[7] Moster, D., Lie, R. T., Irgens, L. M., Bjerkedal, T., & Markestad, T. (2001). The association of Apgar score with subsequent death and cerebral palsy: A population-based study in term infants. *Journal of Pediatrics, 138*(6), 798-803.

[8] Martin, J. A., Wilson, E. C., Osterman, M. J. K., Saadi, E. W., Sutton, S. R., & Hamilton, B. E. (2013). Assessing the quality of medical and health data from the 2003 birth certificate revision: Results from two states. *National Vital Statistics Reports, 62*(2). http://www.cdc.gov/nchs/data/nvsr/nvsr62/nvsr62_02.pdf

[9] Reichman, N. E., & Hade, E. M. (2001). Validation of birth certificate data: A study of women in New Jersey's HealthStart Program. *Annals of Epidemiology, 11*(3), 186-193.

home birth was 0.9 (95% CI 0.2-3.3), while the rate for multiparous women was 0.1 (95% CI 0.0-0.9) (Birthplace, 2011). The rate of early neonatal death was 0.4 (95% CI 0.1-2.4) among primiparas and 0.3 (95% CI 0.1-1.3) for multiparas (Birthplace, 2011). Hutton (2009) conducted a retrospective matched cohort study of planned home birth in Ontario, Canada. They reported that the proportion of non-anomalous perinatal deaths (stillbirth to 28 days) for primiparous (0.2%) vs. multiparous women (0.1%) was the same for both planned home and hospital birth (Hutton, 2009). The total number of non-anomalous perinatal deaths was small, with nine among primiparous women and six among multiparas (Hutton, 2009). A large retrospective, national study from the Netherlands by de Jonge and colleagues (de Jonge, 2015) found that for primiparous women planning home birth, 1.02% experienced perinatal death (stillbirths and neonatal deaths up to 28 days) compared to 1.09% planning a hospital birth, with an adjOR of 0.99 (95% CI 0.79-1.24). Among multiparous women the comparable figures were 0.59% vs. 0.58%, with an adjOR of 1.16 (95% CI 0.87-1.55) (de Jonge, 2015).

Summary – New Evidence Search

In summary, the additional literature review found that rates of cesarean delivery are lower for both primiparous and multiparous women planning a home birth compared to a hospital birth. Neonatal risks varied across studies. Among comparative studies, two reported a slightly higher perinatal mortality risk for nulliparous women planning a home birth compared to a hospital birth and one reported a slightly lower risk at home compared to hospital. These three comparative studies were from three different countries and the only U.S. study to report perinatal mortality by parity was not comparative. Estimates of perinatal mortality are unstable because of small numbers of this fortunately rare outcome. Among the four studies in Table 2 there were 677 occurrences of perinatal death among 817,812 total births (0.82%). Comparisons are limited by differences in outcome and population definitions, differences among OOH birth provider training and regulation, differences among risk status of women planning home birth, and differences among health systems. Because of all these factors and the low quality of available evidence, we cannot exclude a small increase in perinatal risk, particularly for nulliparous women who choose to plan a home birth rather than a hospital birth. However, available evidence indicates that the absolute risk is small, particularly among low-risk women and in situations where there are well-trained OOH birth attendants and functioning systems for consultation and transfer to higher levels of care when the need arises.

Guidelines

The NICE guideline on intrapartum care in healthy women was published in December 2014. The guideline recommends the following regarding place of birth:

Women at low risk of complications

1.1.1 Explain to women who are at low risk of complications that giving birth is generally very safe for both the woman and her baby. [new 2014]

1.1.2 Explain to both multiparous and nulliparous women that they may choose any birth setting (home, freestanding midwifery unit, alongside midwifery unit or obstetric unit), and support them in their choice of setting wherever they choose to give birth: [new 2014]

- Advise low-risk multiparous women that planning to give birth at home or in a midwifery-led unit (freestanding or alongside) is particularly suitable for them because the rate of interventions is lower and the outcome for the baby is no different compared with an obstetric unit. [new 2014]

- Advise low-risk nulliparous women that planning to give birth in a midwifery-led unit (freestanding or alongside) is particularly suitable for them because the rate of interventions is lower and the outcome for the baby is no different compared with an obstetric unit. Explain that if they plan birth at home there is a small increase in the risk of an adverse outcome for the baby. [new 2014]

1.1.3 Using Tables 3 and 4, explain to low-risk multiparous women

- Planning birth at home or in a freestanding midwifery unit is associated with a higher rate of spontaneous vaginal birth than planning birth in an alongside midwifery unit, and these 3 settings are associated with higher rates of spontaneous vaginal birth than planning birth in an obstetric unit

- Planning birth in an obstetric unit is associated with a higher rate of interventions, such as instrumental vaginal birth, caesarean section and episiotomy, compared with planning birth in other settings

- There are no differences in outcomes for the baby associated with planning birth in any setting. [new 2014]

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Table 3. Rates of spontaneous vaginal birth, transfer to an obstetric unit, and obstetric interventions for each planned place of birth: low-risk multiparous women

	Number of incidences per 1,000 multiparous women giving birth			
	Home	**Freestanding midwifery unit**	**Alongside midwifery unit**	**Obstetric unit**
Spontaneous vaginal birth	984	980	967	927
Transfer to an obstetric unit	115	94	125	10**
Regional anesthesia (epidural and/or spinal)***	28	40	60	121
Episiotomy	15	23	35	56
Cesarean birth	7	8	10	35
Instrumental birth (forceps or ventouse)	9	12	23	38
Blood transfusion	4	4	5	8

Table 4. Outcomes for the baby for each planned place of birth: low-risk multiparous women

	Number of babies per 1,000 births			
	Home	**Freestanding midwifery unit**	**Alongside midwifery unit**	**Obstetric unit**
Babies without serious medical problems	997	997	998	997
Babies with serious medical problems	3	3	2	3

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1.1.4 Using Tables 5 and 6, explain to low-risk nulliparous women that:

- Planning birth at home or in a freestanding midwifery unit is associated with a higher rate of spontaneous vaginal birth than planning birth in an alongside midwifery unit, and these 3 settings are associated with higher rates of spontaneous vaginal birth than planning birth in an obstetric unit
- Planning birth in an obstetric unit is associated with a higher rate of interventions, such as instrumental vaginal birth, caesarean section and episiotomy, compared with planning birth in other settings
- There are no differences in outcomes for the baby associated with planning birth in an alongside midwifery unit, a freestanding midwifery unit or an obstetric unit
- Planning birth at home is associated with an overall small increase (about 4 more per 1,000 births) in the risk of a baby having a serious medical problem compared with planning birth in other settings.

Table 5. Rates of spontaneous vaginal birth, transfer to an obstetric unit, and obstetric interventions for each planned place of birth: low-risk nulliparous women

	Number of incidences per 1,000 nulliparous women giving birth			
	Home	**Freestanding midwifery unit**	**Alongside midwifery unit**	**Obstetric unit**
Spontaneous vaginal birth	794	813	765	688
Transfer to an obstetric unit	450	363	402	10
Epidural	218	200	240	349
Episiotomy	165	165	216	242
Cesarean birth	80	69	76	121
Instrumental birth (forceps or ventouse)	126	118	159	191
Blood transfusion	12	8	11	16

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Table 6. Outcomes for the baby for each planned place of birth: low-risk nulliparous women

	Number of babies per 1,000 births			
	Home	**Freestanding midwifery unit**	**Alongside midwifery unit**	**Obstetric unit**
Babies without serious medical problems	991	995	995	995
Babies with serious medical problems	9	5	5	5

Medical conditions and other factors that may affect planned place of birth

1.1.10 Use tables 7, 8, 9 and 10 as part of an assessment for a woman choosing her planned place of birth:

- Tables 7 and 8 show medical conditions or situations in which there is increased risk for the woman or baby during or shortly after labour, where care in an obstetric unit would be expected to reduce this risk.
- The factors listed in tables 9 and 10 are not reasons in themselves for advising birth within an obstetric unit, but indicate that further consideration of birth setting may be required.
- Discuss these risks and the additional care that can be provided in the obstetric unit with the woman so that she can make an informed choice about planned place of birth. [2007, amended 2014]

Table 7. Medical conditions indicating increased risk suggesting planned birth at an obstetric unit

Disease Area	Medical Condition
Cardiovascular	• Confirmed cardiac disease • Hypertensive disorders
Respiratory	• Asthma requiring an increase in treatment or hospital treatment • Cystic fibrosis
Haematological	• Haemoglobinopathies – sickle-cell disease, beta-thalassaemia major • History of thromboembolic disorders • Immune thrombocytopenia purpura or other platelet disorder or platelet count below 100,000 • Von Willebrand's disease

Disease Area	Medical Condition
	• Bleeding disorder in the woman or unborn baby • Atypical antibodies which carry a risk of haemolytic disease of the newborn
Endocrine	• Hyperthyroidism • Diabetes
Infective	• Risk factors associated with group B streptococcus whereby antibiotics in labour would be recommended • Hepatitis B/C with abnormal liver function tests • Carrier of/infected with HIV • Toxoplasmosis – women receiving treatment • Current active infection of chicken pox/rubella/genital herpes in the woman or baby • Tuberculosis under treatment
Immune	• Systemic lupus erythematosus • Scleroderma
Renal	• Abnormal renal function • Renal disease requiring supervision by a renal specialist
Neurological	• Epilepsy • Myasthenia gravis • Previous cerebrovascular accident
Gastrointestinal	• Liver disease associated with current abnormal liver function tests
Psychiatric	• Psychiatric disorder requiring current inpatient care

Table 8. Other factors indicating increased risk suggesting planned birth at an obstetric unit

Factor	Additional Information
Previous complications	• Unexplained stillbirth/neonatal death or previous death related to intrapartum difficulty • Previous baby with neonatal encephalopathy • Pre-eclampsia requiring preterm birth • Placental abruption with adverse outcome • Eclampsia • Uterine rupture • Primary postpartum haemorrhage requiring additional treatment or blood transfusion • Retained placenta requiring manual and/or surgical removal in theatre Caesarean section • Shoulder dystocia

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Factor	Additional Information
Current pregnancy	• Multiple birth • Placenta praevia • Pre-eclampsia or pregnancy-induced hypertension • Preterm labour or preterm prelabour rupture of membranes Placental abruption • Anaemia – haemoglobin less than 8.5 g/dl at onset of labour • Confirmed intrauterine death • Induction of labour • Substance misuse • Alcohol dependency requiring assessment or treatment • Onset of gestational diabetes • Malpresentation – breech or transverse lie • Body mass index at booking of greater than 35 kg/m2 Recurrent antepartum haemorrhage • Small for gestational age in this pregnancy (less than fifth centile or reduced growth velocity on ultrasound) • Abnormal fetal heart rate/Doppler studies • Ultrasound diagnosis of oligo-/polyhydramnios
Previous gynaecological history	• Myomectomy • Hysterotomy

Table 9. Medical conditions indicating individual assessment when planning place of birth

Disease Area	Medical Condition
Cardiovascular	• Cardiac disease without intrapartum implications
Haematological	• Sickle-cell trait • Thalassaemia trait • Atypical antibodies not putting the baby at risk of haemolytic disease • Anemia – haemoglobin 8.5-10.5 g/dl at onset of labor
Infective	• Hepatitis B/C with normal liver function tests
Immune	• Nonspecific connective tissue disorders
Endocrine	• Unstable hypothyroidism such that a change in treatment is required

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Skeletal/Neurological	• Spinal abnormalities • Previous fractured pelvis • Neurologic deficits
Gastrointestinal	• Liver disease without current abnormal liver function • Crohn's disease • Ulcerative colitis

Table 10. Other factors indicating individual assessment when planning place of birth

Factor	Additional Information
Previous complications	• Stillbirth/neonatal death with a known non-recurrent cause • Pre-eclampsia developing at term • Placental abruption with good outcome • History of previous baby more than 4.5 kg • Extensive vaginal, cervical, or third- or fourth-degree perineal trauma • Previous term baby with jaundice requiring exchange transfusion
Current pregnancy	• Antepartum bleeding of unknown origin (single episode after 24 weeks of gestation) • Body mass index at booking of 30–35 kg/m2 • Blood pressure of 140 mmHg systolic or 90 mmHg diastolic or more on two occasions • Clinical or ultrasound suspicion of macrosomia • Para 4 or more • Recreational drug use • Under current outpatient psychiatric care • Age over 35 at booking
Fetal indications	• Fetal abnormality
Previous gynaecological history	• Major gynaecological surgery • Cone biopsy or large loop excision of the transformation zone • Fibroids

Service organization and clinical governance

1.1.15 Ensure that all women giving birth have prompt access to an obstetric unit in case they need transfer of care for medical reasons or because they request regional analgesia. [new 2014]

1.1.16 Ensure that there are

- robust protocols in place for transfer of care between settings (see also section 1.6). [new 2014]
- clear local pathways for the continued care of women who are transferred from one setting to another, including:

- when crossing provider boundaries
- if the nearest obstetric or neonatal unit is closed to admissions or the local midwifery-led unit is full [new 2014]

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Risk criteria for planned home birth

The 2014 NICE draft guideline for antepartum care clearly outlines conditions that make a woman high-risk. In addition, the Oregon Public Health Division referenced a report from the American College of Obstetrics and Gynecology (ACOG) on Planned Home Birth[10] as their published criteria for being low-risk. This includes the following requirements:

- Gestational age ≥ 36 weeks and ≤41 completed weeks of pregnancy
- Singleton
- Vertex position
- Absence of preexisting or pregnancy-related maternal disease

The ACOG committee opinion references Hutton 2006 and Janssen 2009 as a source for these criteria. They also note that the low-risk criteria utilized in these two observational studies did not exclude women with a prior cesarean section; however, because of potential risks they state that ACOG "considers a prior cesarean delivery to be an absolute contraindication to planned home birth". They also note that studies showing favorable perinatal outcomes (de Jonge 2009; Hutton 2006; Janssen 2009) were conducted in settings that have "highly integrated health care systems with established criteria and provisions for emergency intrapartum transport." Therefore, ACOG "believes that the availability of timely transfer and an existing arrangement with a hospital for such transfers is a requirement for consideration of a home birth."

The final report of the Licensed Direct Entry Midwife (LDM) Staff Advisory Workgroup also recommends that planned home birth be limited to patients who are low-risk, defined as pregnancies that do not have any of the following characteristics:

- Presentation other than cephalic
- Previous cesarean delivery
- Gestational age < 36 or > 43 weeks
- Multiple gestations
- Diabetes/uncontrolled gestational diabetes or gestational diabetes controlled with medication
- Pre-eclampsia

Current Oregon law[11] outlines risk criteria which birthing centers must follow. A proposed rule would apply those same criteria to home births. Those criteria can be found in Appendix A.

All three observational studies included in this document were based on registries in countries or provinces that strictly control the practice of midwifery and adhere to established criteria for planned home birth. All three lists of criteria are provided in Appendix A.

[10] American College of Obstetricians and Gynecologists. (2011). Planned home birth. Committee Opinion No. 476. *Obstetrics & Gynecology*, *117*, 425–428.
[11] http://arcweb.sos.state.or.us/pages/rules/oars_300/oar_333/333_076.html

Midwifery certification

Training and certification requirements for midwives vary among the countries referenced in this document. A summary is presented below:

The Netherlands[12]

"The midwifery training is a four year fulltime direct entry education, which eventually leads to a Bachelor's degree. The total study load is 240 ECTS and equals nearly 6,800 hours of education. Altogether, there are two years of theory, one year of primary care internships, and one year of secondary and tertiary care internships. The internships are spread equally over these four years. Students are primarily trained to become independent primary care midwives. 190 Students enroll each year nationwide. They have had an extensive assessment, which selects the best candidates. Around three times more candidates apply for the course than places are available."

British Columbia[13]

"All current CMBC approved programs are Canadian four year direct-entry education programs leading to a university degree, or bridging programs leading to equivalency."

Ontario[14]

"1. The applicant must have at least one of the following:

- A baccalaureate degree in health sciences (midwifery) from a university in Ontario.
- A degree, diploma or certificate from a program listed in Schedule 1.
- Qualifications that are equivalent to the degree referred to in subparagraph i, as determined by the Council or by a body or bodies designated by the Council.

2. The applicant must:

- Have current clinical experience consisting of active practice for at least two years out of the four years immediately before the date of the application, and
- Have attended at least 60 births, of which at least:
    - 40 were attended as primary midwife
    - 30 were attended as part of the care provided to a woman in accordance with the principles of continuity of care
    - 10 were attended in hospital, of which at least five were attended as primary midwife, and
    - 10 were attended in a residence or remote clinic or remote birth centre, of which at least five were attended as primary midwife

3. The applicant must have successfully completed the qualifying examination that was set or approved by the Registration Committee at the time the applicant took the examination."

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[12] http://www.nurse.or.jp/nursing/international/icm/report/data/2012/icm-dutch.pdf
[13] http://www.cmbc.bc.ca/pdf.shtml?Exploring-Midwifery-as-a-Career
[14] http://www.e-laws.gov.on.ca/html/source/regs/english/2011/elaws_src_regs_r11168_e.htm

United Kingdom[15]

Midwifery degree

- Students are awarded both an academic and a professional qualification, through integrated study of theory and supervised midwifery practice
- Supervised midwifery practice is 50% of the program and takes place in both community and hospital settings, including antenatal clinics and wards, labour wards, postnatal wards and neonatal care
- The programs are normally three years in length and studied on a full-time basis

Oregon[16]

Mandatory licensure of direct entry midwives in Oregon was established in 2013 with passage of House Bill 2997, which requires any direct entry midwife practicing after January 1, 2015, to hold a license. The Oregon Board of Direct Entry Midwifery already requires that LDMs hold a certified professional midwife (CPM) credential from the North American Registry of Midwives, complete an examination, be certified in infant and adult cardiopulmonary resuscitation, have a written plan for transport of the patient, hold a high school diploma (or equivalent), and attend and participate in, at a minimum:

- Twenty-five assisted deliveries
- Twenty-five deliveries for which the LDM applicant was the primary care provider
- One hundred prenatal care visits
- Twenty-five newborn examinations, and
- Forty postnatal examinations

North American Registry of Midwives (NARM)[17]

There are multiple routes to certification by the NARM, but in general they include a written test, a skills assessment test, and the following experience requirements:

Phase 1: Births as an Observer

- Ten births in any setting, in any capacity

Phase 2: Clinicals as Assistant under Supervision

- Twenty births, 25 prenatal exams, 20 newborn exams, 10 postpartum visits

Phase 3: Clinicals as Primary under Supervision

- Twenty births, 75 prenatal visits, 20 newborn exams, and 40 postpartum exams

It is also required that the applicant have a preceptor(s) that attests to the applicant's proficiency on "skills, knowledge, and abilities essential for competent practice" and that the applicant be certified in Adult CPR, and Neonatal Resuscitation Certification.

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[15] http://www.nhscareers.nhs.uk/explore-by-career/midwifery/training-to-be-a-midwife/
[16] http://www.oregon.gov/OHLA/DEM/Pages/Midwifery_How_to_Get_Licensed.aspx
[17] http://narm.org/entry-level-applicants/

Oregon data on planned out-of-hospital birth

In 2013 the Oregon Public Health Division published its first report on birth outcomes by planned birth place and attendant. Because this report specifically addresses home birth outcomes in the state of Oregon, a summary is presented here.

In 2011, the Oregon Legislature passed House Bill 2380, which required the Oregon Public Health Division to add two questions to the Oregon Birth Certificate to determine planned place of birth and birth attendant, and to report annually on birth outcomes, including death, by location and attendant type. The specific questions were: "Did you go into labor planning to deliver at home or at a freestanding birthing center? If yes, what was the planned primary attendant type at the onset of labor?" In addition, for 2012, the Oregon Public Health Division conducted a special study of deaths in term infants (≥ 37 weeks' gestation) intended to deliver out-of-hospital. The perinatal fatality analysis includes fetal and early neonatal deaths ≥ 37 weeks' estimated gestational age through the first 6 days of life.

During 2012, 42,011 live term births occurred in Oregon. Of these 2,021 (4.8%) planned an out-of-hospital birth (home birth or freestanding birthing center).

Key findings of term fetal and early neonatal deaths by planned place of birth and planned birth attendant include the following:

- Sixty-two term (≥ 37 weeks' gestation) fetal deaths occurred in Oregon during 2012; 4 (6.5%) of these occurred among planned out-of-hospital births.
- Thirty term early neonatal deaths (during the first 6 days of life) occurred in Oregon during 2012; 4 (13.3%) of these occurred among planned out-of-hospital births.
- In total, 92 term fetal and early neonatal deaths occurred in Oregon during 2012; 8 (8.7%) occurred among planned out-of-hospital births. These 8 deaths underwent a fetal and neonatal mortality case review per published national guidelines.

Key findings of the perinatal fatality case review of term births planned to occur out-of-hospital include the following:

- Four term fetal and four early neonatal deaths occurred during 2012 among women who planned to deliver out-of-hospital
- Planned birth attendants: Certified Nurse Midwife (1), Licensed Direct-Entry Midwives (4), Unlicensed Midwife (1), Undetermined Licensure Midwife (1), and Naturopathic Physician (1)
- Median birth weight (3515 grams)
- Maternal characteristics were similar to the larger group of planned out-of-hospital births
- Two pregnancies had inadequate or no prenatal care
- Chart review noted that, among perinatal deaths:
    - Two pregnancies were twin gestations

    - Four mothers declined prenatal ultrasound (to confirm gestation and identify pathology)
    - Five mothers declined Group B streptococcal testing (to identify women who are carriers of GBS; treatment during labor is recommended to decrease the risk of early GBS neonatal sepsis)
    - Two mothers declined prophylaxis during labor for Group B streptococcal positive tests
- Six of eight transferred to the hospital during labor:
    - Indications for transfer to a hospital from home or birthing center included (multiple causes may apply): loss of fetal heart tones (3), prolonged labor (2), decreased fetal movement (2), and malpresentation (2)
    - One mother initially declined transfer during labor despite recommendation by birth attendant
- Six of eight pregnancies did not meet published low-risk criteria for out-of-hospital birth*:
    - More than 41 weeks gestation (4)
    - Twin gestation (2)
    - Morbid obesity (> 40 BMI) (1)
    - Planned attendants among these 6: Certified Nurse Midwife (1), Licensed Direct-Entry Midwives (3), Unlicensed Midwife (1), and Naturopathic Physician (1)
- Causes of death and major contributing factors (more than one may apply):
    - Hypoxic ischemic encephalopathy or cardiorespiratory failure (lack of blood flow) (3)
    - Chorioamnionitis (infection in the womb) (3)
    - Pre-existing or pregnancy-related maternal disease (2)
    - Respiratory failure (1)
    - Undetermined, umbilical cord wrapped around neck, large baby (1)
    - Undetermined, twin gestation, small baby (2)

The term perinatal mortality rate for planned out-of-hospital births (4.0/1,000 pregnancies) was nearly twice that of in-hospital births (2.1/1,000). When excluding those pregnancies that did not meet published criteria for being low risk, the perinatal mortality rate for planned out-of-hospital births is 1.0/1000.

EVIDENCE SUMMARY

The evidence pertaining to home birth from randomized trials is extremely sparse, limited to just 12 participants, and hence an insufficient evidence base from which to draw conclusions. The largest observational studies suggest that home birth results in significantly fewer obstetrical interventions and maternal adverse outcomes. The evidence pertaining to neonatal outcomes is less clear; while one

meta-analysis found an elevated risk of neonatal death, this was not true when the analysis was limited to studies in which the attendant was either a certified midwife or certified nurse midwife. Observational studies conducted in settings where there are clear criteria for appropriateness of home birth, differing regulatory and training requirements, and systems of care (e.g., Canada, the Netherlands) do not find an elevated neonatal death rate. The NICE guideline's evidence review (based on the Birthplace study) found that there is a slightly increased risk of adverse neonatal events for primiparous women, but the NICE panel still suggesteds that these women be eligible for planned home birth after participating in informed decision-making using risk tables.

The new search and evidence summary done at the request of the EbGS at the April 2, 2015 meeting found that the absolute risk of perinatal mortality is very low overall, but that there are few U.S.-based studies, that evidence quality is low at best, and that available studies provide conflicting estimates of perinatal mortality risk. However,an elevated risk of perinatal mortality, particularly among primiparous women, cannot be ruled out by current research. This is in alignment with the findings of the Birthplace study (2011) on which the NICE guideline was based and generally supports that guideline's conclusions of offering home birth to low-risk women who have participated in informed decision-making.

In their first year of reporting, evidence from the State of Oregon Public Health Department identified an elevated risk of perinatal death in pregnancies with a planned home delivery. However, when excluding those pregnancies that did not meet published criteria for being low- risk, the rate is not elevated compared to planned hospital births.

Criteria for low-risk pregnancy at the time of labor and delivery have been established by national or provincial governments as well as by US national and state provider organizations. These criteria have varying levels of detail, but each has criteria for consultation with other providers, indications requiring hospital birth and indications requiring transfer of care.

Good outcomes for planned out-of-hospital birth have been demonstrated in several countries. However, these settings have system characteristics that help to maximize safety. Chief among these is a robust system of consultation and referral/transfer that can assure seamless care for the woman and her newborn when transfer is needed. In addition, these systems include thorough education (informed consent) of women and families about the potential need for consultation/referral/transfer and the potential risks associated with having a delay to receipt of emergency obstetric and neonatal care. Consideration of distance and time from a hospital able to provide emergency obstetric and neonatal services is important in managing intrapartum complications and in providing fully informed consent. Another characteristic is written agreements that cover consultation/referral/transfer and a well-defined and practiced system of transfer. Out-of-hospital birth attendants in these systems are appropriately trained and experienced in the identification and management of obstetric and neonatal emergencies, and are also licensed and certified. These providers should be capable of initiating appropriate newborn resuscitation, and be able to provide standard newborn care in addition to the routine postpartum care of women. Certification requirements for the practice of midwifery can vary significantly between the U.S. and other countries, with U.S. requirements for midwives, other than CNM/CMs, generally being less rigorous with regard to both years of formal education and experience.

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GRADE-Informed Framework

The HERC develops recommendations by using the concepts of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for carrying out the steps involved in developing recommendations. There are four elements that determine the strength of a recommendation, as listed in the table below. The HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Balance between desirable and undesirable effects, and quality of evidence, are derived from the evidence presented in this document, while estimated relative costs, values and preferences are assessments of the HERC members.

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
Planned out-of-hospital birth for low-risk pregnancies	Include fewer intrapartum interventions and cesarean births (common outcome). Mixed results on neonatal outcomes, including potential increased risk of fetal/neonatal death (very rare outcome), particularly for primiparous	Very low to low based on 15 observational studies. Risk of bias generally acceptable, but some studies had marked limitations. Many studies downgraded because of indirectness due to different	Low. (favors out of hospital birth)	Low (women planning out-of-hospital birth prefer a non-hospital setting)	Recommended for coverage (*weak recommendation)*	There is low quality, but consistent evidence of benefit and lower quality evidence of significant, rare harms, including increased perinatal mortality. Women choosing out-of hospital birth have strong values and preferences toward this choice, despite the potential risk of significant harm. Additional evidence search and summary

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
	women.	country and context of study.				results in no change in weak recommendation for coverage.
Planned out-of-hospital birth for unselected pregnancies (including those with unknown or known high risk factors)	Possible lower maternal morbidity, increased fetal/neonatal mortality	Very low based on one systematic review of 12 studies (downgraded to very low because of internal and external validity concerns). Additional evidence search and summary also found very low-quality evidence suggesting increased risk for pregnancy	Moderate. Increased risk of poor outcomes leading to increased medical and societal costs.	Low (women planning out-of-hospital birth prefer a non-hospital setting)	Not recommended for coverage *(strong recommendation)*	Based on very low evidence that suggests increased fetal/neonatal mortality, increased resources (for associated harms), and rapidity of evolution of complications (e.g. uterine rupture). This leads to a strong recommendation against coverage, despite values and preferences that lead some women to choose this despite potential harms.

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Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
		complicated by maternal diseases, breech, multiple gestation and TOLAC.				

*The Quality of Evidence rating was assigned by the primary evidence source for initial literature search (not the HERC Subcommittee), and determined for critical and important outcomes for each individual study included in the new evidence search,

Note: GRADE framework elements are described in Appendix B

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POLICY LANDSCAPE

Quality measures

No pertinent quality measures were identified when searching the National Quality Measures Clearinghouse.

Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

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APPENDIX A. RISK CRITERIA FOR PLANNED HOME BIRTH

Oregon birth center absolute risk criteria

Risk factors that if present **on admission** to the birthing center for labor and delivery, would prohibit admission to the birthing center

- Current substance abuse which has the potential to adversely affect labor and/or the infant
- Quadriplegia
- Hypertension >150/100 on at least two occasions
- For this pregnancy, Type I Diabetes, other diabetes requiring insulin to maintain acceptable control, or Type II Diabetes
- Thrombosis, active/current
- Severe anemia, <9 hemoglobin
- Uncontrolled seizure disorder
- Life-threatening congenital defects in fetus. This does not include documented lethal anomalies
- History of previous uterine wall surgery, including Caesarean section, if one or more of the following risk factors is present:
    - Conception occurred < 12 months following that surgery or uterine procedure;
    - Absence of ultrasound to rule out placenta previa and/or placental attachment to the surgical site;
    - History of two or more Caesarean sections without a prior successful vaginal delivery;
    - History of myomectomy which invaded the endometrium;
    - History of a known uterine perforation;
    - History of Caesarean section which included classical incision;
    - History of Caesarean section and complications including postoperative infection, diabetes, or steroid use;
    - Absence of signed, detailed informed consent

NOTE: Any woman with previous uterine wall surgery must be evaluated for the presence of risk factors, and must go through an informed consent process. The Information given to the woman must include an explanation of the risk; including non-absolute risks, of a vaginal birth after Caesarean section, and an explanation of the contingency plan in place should transport be necessary. If transport becomes necessary, the birthing center should notify the receiving facility when the transport is imminent.

- Need for Caesarean delivery this birth
- Multiple gestation without reassuring bio-physical profile of greater than or equal to 8 out of 10
- No previous prenatal care or written prenatal records available
- Abnormal fetal surveillance studies
- Fetal presentation other than vertex, when known
- Rising antibody titre -types known to affect fetal well-being; significant Rh sensitization
- Amniotic fluid index >30 at term
- Amniotic fluid index <5 without reassuring labor progress, without reassuring fetal heart tones and/or abnormal non- stress test
- Abnormal bleeding

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- Need for chemical and/or pharmacological induction of labor
- Need for general or conduction anesthesia
- Eclampsia; preeclampsia with lab abnormalities
- Low-lying placenta within 2 cm. or less of cervical os; vasa previa; complete placenta previa; abruption placenta
- Genital herpes, primary; secondary uncoverable at onset of labor
- Labor or premature rupture of membranes at <36 weeks; pregnancy >43 weeks or >42 weeks with abnormal non- stress test
- Chorioamnionitis
- Thick meconium-stained amniotic fluid without reassuring Doppler heart tones
- Known pre-term fetal demise

Risk factors that if they develop **during labor and delivery**, require transfer of the client to a higher level of care

- Failure to progress in active labor with strong contractions and/or maternal/fetal compromise
- Abnormal fetal heart tone (FHT) pattern unresponsive to treatment; inability to auscultate fetal heart tones unless birth is imminent
- Thick meconium-stained amniotic fluid without reassuring Doppler heart tones and birth is not imminent
- Hypertension> 150/1 00 on at least two occasions
- Abnormal bleeding
- Prolapsed umbilical cord
- Fetal presentation other than vertex, when known, and birth is not imminent
- Multiple gestation when birth is not imminent
- Amniotic fluid index <5 without reassuring labor progress or without reassuring fetal heart tones or abnormal non-stress test
- Persistent fever of equal to or greater than 101 degrees Fahrenheit (oral) or indication of serious infection with the potential to harm the mother or the fetus
- Development of severe medical or surgical problem

Risk factors that, if they develop **during the postpartum period** in the mother or infant, would require transfer to a higher level of care

Mother

- Abnormal bleeding unresponsive to treatment and/or symptoms of hypovolemia
- Need for transfusion
- Retained placenta or incomplete placenta, with bleeding; suspected placenta accreta; retained placenta> 3 hours

Other

- Hypertension >150/100 on at least two occasions
- Shock, unresponsive to treatment
- Laceration requiring repair in a hospital

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- Enlarging hematoma
- Development of preeclampsia or eclampsia
- Signs or symptoms of serious infection

Infant

- Apgar problems <5 at 5 minutes or <7 at 10 minutes
- Inability to maintain [axillary] temperature between 97 degrees Fahrenheit and 100 degrees Fahrenheit at 2 hours
- Hypotonia >10 minutes
- Tremors, seizures, or hyperirritability
- Life-threatening congenital defects in fetus. This does not include documented lethal abnormalities; (in the presence of known and documented lethal fetal abnormalities, the denial of admission and the requirements to transfer do not apply)
- Respiratory or cardiac irregularities (examples: abnormal capillary refill time, disturbance of rate or rhythm; grunting or retracting after 30 minutes postpartum, need for oxygen> 30 minutes without improvement; cyanosis, central and persistent)
- Signs/symptoms of infection

Final report of the Obstetric Working Group of the National Health Insurance Board of the Netherlands (abridged version)

What follows is the list of specific obstetric indications, including an explanation of the description of the obstetrical care provider and guidelines on how to deal with the consultative situation.

The obstetric indication list is divided into six main groups, within which reference is made to the various obstetric and medical disorders and diseases. Where necessary, an explanation is provided about the obstetric policy related to specific indications and upon what the referral policy is based. The right-hand column shows for each indication who is the most suitable care provider.

The main purpose of the indication list is to provide a guide for risk-selection. The primary obstetric care provider, midwife, or GP is primarily responsible for this risk-selection. The Manuel is a consensus document showing the agreement reached by the professional groups on their decision-making structure.

Explanation of the codes used for the care providers

Code	Description	Care provider
A Primary obstetric care	The responsibility for obstetric care in the situation described is with the primary obstetric care provider.	Midwife/G.P.
B Consultation situation	This is a case of evaluation involving both primary and secondary care. Under the item concerned, the individual situation of the pregnant woman will be evaluated and agreements will be made about the responsibility for	Depending on Agreements

Code	Description	Care provider
	obstetric care (see Section 4.5).	
C Secondary obstetric care	This is a situation requiring obstetric care by an obstetrician at secondary level for as long as the disorder continues to exist.	Obstetrician
D Transferred primary obstetric care	Obstetric responsibility remains with the primary care provider, but in this situation it is necessary that birth takes place in a hospital in order to avoid possible transport risk during birth.	Midwife/G.P.

1. Pre-existing disorders – non-gynaecological

In cases of pre-existing disorders that are relevant to obstetrics, other care providers other than the midwife are regularly involved with care of the pregnant woman. In cases requiring consultation, it is necessary to involve the other care providers in the consultation.

For this reason, in disorders given code B in this section, attention should be given to collaboration with others outside the field of obstetrics. Attention should be paid to the counselling of women who are considering the possibility of becoming pregnant.

1.1	Epilepsy, without medication	A
1.2	Epilepsy, with medication Prenatal diagnostics are recommended in connection with the disorder and its medication. Optimal care requires consultation between all care providers concerned (midwife, G.P, obstetrician, neurologist).	B
1.3	Subarachnoid haemorrhage, aneurysms Care during puerperium can be at primary level.	C
1.4	Multiple sclerosis Depending upon the neurological condition, a complicated delivery and the possibility of urine retention should be taken into account. For optimal care, consultation between all care providers concerned is indicated.	B
1.5	Hernia nuclei pulposi This represents a C-situation in cases of a recently suffered HNP or where there are still neurogenic symptoms. It is an A-situation after treated hernia, especially if a previous pregnancy was normal. Both the medical history and the current clinical condition are relevant.	A/ C
1.6	Lung function disorder The opinion of the lung specialist should be taken into account during evaluation.	B

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1.7	Asthma Care during pregnancy, birth and puerperium can only take place at a primary level when the asthma involves lengthy symptom-free intervals, whether or not use is made of inhalation therapy. Consultation with the GP/specialist involved is recommended.	A/ C
1.8	Tuberculosis, active Tuberculosis, non-active In cases of an active tuberculoses process and subsequent treatment, consultation should take place with the physician involved and the obstetrician regarding the clinical condition and care during pregnancy and birth. In cases of non-active tuberculosis, care during pregnancy and birth can take place at a primary level.	C A
1.9	HIV-infection As a result of the current possibilities of medical therapy for preventing vertical transmission, these patients should be cared for during pregnancy and birth in a hospital equipped for the treatment of HIV and AIDS.	C
1.10	Hepatitis B with positive serology (Hbs-AG+) Since 1988 it is important that a screening programme for this serology is carried out on pregnant women.	A
1.11	Hepatitis C Consultation with the obstetrician and follow-up by the pediatrician is recommended.	B
1.12	A heart condition with haemodynamic consequences Pregnancy and birth will have an effect on the pre-existing haemodynamic relationships. A cardiac evaluation is important.	C
1.13	Thrombo-embolic process Of importance are the underlying pathology and the presence of a positive family medical history. Pre-conceptual counselling is important.	B
1.14	Coagulation disorders	C
1.15	Renal function disorders When there is a disorder in renal function, with or without dialysis, referral to secondary care is recommended.	C
1.16	Hypertension Pre-existing hypertension, with or without medication therapy, will require referral to secondary care. Hypertension has been defined by the ISSHP as: A single event of diastolic blood pressure of 110 mm Hg or more (Korotkoff IV). Diastolic blood pressure of 90 mm Hg or more at two subsequent blood pressure measurements with an interval of at least 4 hours between the two measurements. A distinction should be drawn between a	A/ C

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	diastolic blood pressure under 95 mm and a pressure of 95 mm and higher. Extra attention should be paid to a pregnant woman with a diastolic pressure between 90 and 95 mm; from 95 mm, referral to secondary care should take place.	
1.17	Diabetes mellitus	C
1.18	Hyperthyroidism	C
1.19	Hypothyroidism In cases of biochemical euthyroid, without antibodies and without medication, or stable on levothyroxine medication, care can take place at a primary level. Where levothyroxine medication is given, specific tests are recommended due to the frequent increase in medication required during pregnancy.	B
1.20	Anemia, due to a lack of iron Anemia is defined as Hb<6.0 mmol that has existed for some time.	B
1.21	Anemia, other This includes the haemoglobinopathies.	B
1.22	Inflammatory Bowel Disease This includes ulcerative colitis and Crohn's disease.	C
1.23	System diseases and rare diseases These include rare maternal disorders such as Addison's disease and Cushing's disease. Also included are systemic lupus erythematosus (SLE), anti-phospholipid syndrome (APS), scleroderma, rheumatoid arthritis, periarteritis nodosa, Marfan's syndrome, Raynaud's disease and other systemic and rare disorders.	C
1.24	Use of hard drugs (heroin, methadone, cocaine, XTC, etc.) Attention should be paid to actual use. A urine test can be useful even in cases of past use in the medical history. The involvement of the pediatrician is indicated during the follow-up postpartum.	C
1.25	Alcohol abuse The fetal alcohol syndrome is important. The involvement of the pediatrician is indicated during the follow-up postpartum.	C
1.26	Psychiatric disorders Care during pregnancy and birth will depend on the severity and extent of the psychiatric disorder. Consultation with the physician in charge is indicated.	B

2. Pre-existing gynaecological disorders

2.1	Pelvic floor reconstruction This refers to colpo-suspension following prolapse, fistula and previous rupture. Depending on the cause, the operation technique used and the results achieved, the	C

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	obstetrician will determine policy regarding the birth. A primary caesarean section or an early primary episiotomy can be considered, to be repaired by the obstetrician. If the chosen policy requires no special measures and no specific operating skill, then care during birth can be at primary level.	
2.2	Cervical amputation	C
	Cervical cone biopsy	B
	Cryo- and lis-treatment The practical application of obstetric policy in this field can be worked out in local mutual agreements. If an uncomplicated pregnancy and birth have taken place following cone biopsy then a subsequent pregnancy and birth can take place at primary level.	A
2.3	Myomectomy (serous, mucous) Depending on the anatomical relationship, the possibility of a disturbance in the progress of the pregnancy or birth should be taken into account.	B
2.4	Abnormalities in cervix cytology (diagnostics, follow-up) There should be differentiation according to obstetric versus gynaecological policy. Gynaecological consultation can be indicated even without obstetric consequences. Participation in national cervical cancer screenings program is not provided pregnant women. The gynaecological follow-up is not an impediment to obstetric care at primary level.	B/A
2.5	DES-daughter (untreated and under supervision) There should be a differentiation according to obstetric versus gynecological policy. Gynaecological care related to the problems surrounding DES may be necessary, while obstetric care can take place at primary level.	B
2.6	IUD in situ	B
	Status following removal of the IUD	A
2.7	Status following infertility treatment In practice, the wish of the patient to be cared for at secondary level plays a role here, even though the pregnancy and birth are otherwise normal. There is no question of an increased obstetric risk.	A
2.8	Pelvic deformities (trauma, symphysis rupture, rachitis) Consultation should take place at the start of the last trimester. It should be pointed out that care at secondary level has not been shown to have any added value in cases of pelvic instability and symphysis pubis dysfunction.	B
2.9	Female circumcision/Female genital mutilation	A/B

	Circumcision as such can require extra psychosocial care. Where there are serious anatomical deformities, consultation should take place in the third trimester.	

3. Obstetric medical history

3.1	Active blood group incompatibility (Rh, Kell, Duffy, Kidd)	C
	ABO-incompatibility Pregnancy and birth can take place at primary care level in cases of ABO-antagonism, but one should be on the alert for neonatal problems. Consultation is indicated.	B
3.2	Pregnancy induced hypertension in the previous pregnancy	A
	Pre-eclampsia in the previous pregnancy	B
	HELLP-syndrome in the previous pregnancy	C
3.3	Habitual abortion (3 times) If an abortion should occur again, the need to carry out pathological study of fetal material should be discussed. Genetic counselling prior to pregnancy is also advised.	A
3.4	Pre-term birth (<37 weeks) in a previous pregnancy If a normal pregnancy has taken place subsequent to the premature birth, then a further pregnancy can be conducted at primary care level.	B
3.5	Cervix insufficiency (and/or Shirodkar-procedure) Secondary level care during pregnancy is indicated up to 37 weeks; with a full term pregnancy, home birth is allowed. If a subsequent pregnancy was normal, then future pregnancies and deliveries can be conducted at primary care level.	C/A
3.6	Placental abruption	C
3.7	Forceps or vacuum extraction Evaluation of information from the obstetrical history is important. Documentation showing a case of an uncomplicated assisted birth will lead to the management of the present pregnancy and birth at primary care level. Consultation should take place when no documentation is available or when there are signs of a complicated assisted birth.	A/B
3.8	Caesarean section	C
3.9	Fetal growth retardation (Light for date) A birth weight of P<2.3 or obvious neonatal hypoglycemia related to fetal growth retardation.	C
3.10	Asphyxia Defined as an APGAR score of <7 at 5 minutes. It is important to know whether a pediatrician was consulted because of asphyxia at a previous birth.	B

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3.11	Perinatal death Such an obstetrical history requires consultation. It is also important to know whether there was a normal pregnancy following the perinatal death. Pregnancy and birth can then be conducted at primary care level.	B
3.12	Prior child with congenital and/or hereditary disorder It is important to know the nature of the disorder and what diagnostics were carried out at the time. If no disorders can currently be discerned, then further care can be at primary care level.	B
3.13	Postpartum haemorrhage as a result of episiotomy	A
3.14	Postpartum haemorrhage as a result of cervix rupture (clinically demonstrated) The assumption is that there is a chance of a recurrence; the pregnancy and birth can be conducted at primary care level. The decision can be taken to allow birth to take place in the hospital.	D
3.15	Postpartum haemorrhage, other causes (>1000 cc) In view of the chance of a recurrence, although the pregnancy and birth can be conducted at primary care level, the decision can be taken to allow birth to take place in the hospital.	D
3.16	Manual placenta removal in a previous pregnancy In view of the increased recurrence risk, the next following pregnancy and birth can be cared for at primary care level, with the birth taking place in hospital. When the birth following one in which the manual placenta removal has taken place has had a normal course, a subsequent pregnancy and birth can be cared for at primary level. When in the previous birth a placenta accreta is diagnosed, obstetrical care at secondary level is indicated.	D
3.17	4th degree perineal laceration (functional recovery/no functional recovery) If satisfactory functional recovery has been achieved following the 4th degree tear, then pregnancy and birth can be managed at primary care level. The possibility of performing a primary episiotomy during birth should be considered. If secondary repair surgery was necessary, then referral to secondary care is indicated (similarly to that which is stated for pelvic floor reconstruction). If no functional repair has been achieved following a 4th degree tear, then birth should be managed at secondary care level.	A/C
3.18	Symphysis pubis dysfunction There is no added value to managing pregnancy or birth at secondary care level in cases with a symphysis pubis dysfunction in the history or with pelvic instability.	A
3.19	Postpartum depression There is no added value to managing pregnancy or birth at secondary care level in cases with a p.p.d. in the history. Postpartum depression occurs at such a time	A

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	postpartum that even the puerperium can be cared for at primary care level.	
3.20	Postpartum psychosis It is necessary to distinguish whether there is a case of long-term medicine use. It is important to have a psychiatric evaluation of the severity of the psychosis and the risk of recurrence.	A
3.21	Grand multiparty Defined as parity >5. There is no added value to managing a pregnancy and birth at secondary care level.	A
3.22	Post-term pregnancy Post-term pregnancy in the obstetrical history has no predictive value for the course of the current pregnancy and birth.	A

4. Developed/discovered during pregnancy

In this section it is the case that supervision at secondary level care is necessary in situations given the code C, as long as the problem described still exists. If it no longer exists, then the patient can be referred back to primary level care.

4.1	Uncertain duration of pregnancy by amenorrhoea >20 weeks Consultation is required when the duration of pregnancy is uncertain after 20 weeks amenorrhoea. The primary care provider has access to sufficient additional diagnostic tools in the first 20 weeks.	B
4.2	Anemia (Hb<6.0 mmol/l) It is important that the nature and the severity of the anemia are analysed during consultation.	B
4.3	Recurrent urinary tract infections One can speak of recurrent urinary tract infection when an infection has occurred more than twice. Further analysis of the infection is required. The risk of renal function disorders and the risk of pre-term birth are important. The course of further diagnostics can take place within the local mutual agreements made between the three professional groups.	B
4.4	Pyelitis Hospital admission is required for the treatment of pyelitis, so that care will have to be at secondary level. After successful treatment of the pyelitis, further care during pregnancy and birth can be at primary level.	C
4.5	Toxoplasmosis, diagnostics and therapy Referral to secondary level is required both for diagnostics and for therapeutic policy.	C
4.6	Rubella An increased risk of fetal growth retardation, pre-term birth and visual and hearing	C

	disorders should be taken into account in a case of primary infection with rubella during pregnancy.	
4.7	Cytomegalovirus An increased risk of perinatal death and subsequent morbidity should be taken into account.	C
4.8	Herpes genitalis (primary infection) Herpes genitalis (recurrent) During a primary infection there is a (slight) risk of transplacental fetal infection. In the first year after the primary infection, there is a higher frequency of recurrences and asymptotic virus excretion. If a primary infection occurs shortly before or during birth, there is an increased risk of neonatal herpes. Due to the possibility of treatment with antiviral drugs, referral to secondary care is indicated for primary infections. For recurrences and where herpes genitalis is in the medical history, it is advisable to carry out a virus culture from the oropharynx of the neonate. If there are frequent recurrences (>1/month) or where there is a recurrence during birth, referral is indicated due to the increased risk of infection of the neonate. It is as yet not clear whether the presence of antibodies are sufficient protection for the child.	C A
4.9	Parvo virus infection This infection can lead to fetal anemia and hydrops. Possibilities exist for treating these problems.	C
4.10	Varicella/Zoster virus infection This refers to a maternal infection. Primary infection with varicella/zoster virus (chicken pox) during the pregnancy might require treatment of the pregnant woman with VZV-immunoglobulin due to the risk of fetal varicella syndrome. If varicella occurs shortly before birth or early during the puerperium, there is a risk of neonatal infection. Treatment of the mother and child with an antiviral drug is sometimes indicated. If there is a case of manifest herpes zoster (shingles), then there is no risk of fetal varicella syndrome.	B
4.11	Hepatitis B (Hbs-Ag+)	A
4.12	Hepatitis C This is an indication for referral to secondary care for consultation. Attention must be given to follow-up by the pediatrician.	B
4.13	Tuberculosis This refers to an active tuberculous process.	C
4.14	HIV-infection In connection with the present possibilities of medical therapy for preventing vertical transmission, care for these patients during pregnancy and birth should take place in a hospital/center equipped to deal with HIV and AIDS.	C

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4.15	Syphilis Positive serology and treated	A
	Positive serology and not yet treated	B
	Primary infection Attention should be paid to collaboration between the primary and secondary care providers involved during referral. It is important to ensure perfect information exchange between the midwife, the GP, the obstetrician and the venereologist. Structural agreements can be worked out in local collaboration.	C
4.16	Hernia nuclei pulposi, (slipped disk) occurring during pregnancy Policy should be determined according to complaints and clinical symptoms. Where there are no complaints, (further) care can take place at primary level.	B
4.17	Laparotomy during pregnancy As soon as wound healing has occurred and if the nature of the operation involves no further obstetric risks, care for the pregnant woman can return to primary level. During hospitalisation the obstetrician will be involved in the care. If there are no further obstetric consequences then care for the pregnant woman can return to primary level.	C
4.18	Cervix cytology PAP III or higher What is important here is that further gynaecological policy (for the purpose of subsequent diagnostics) may be necessary, while the pregnancy and birth can be conducted at primary level.	B
4.19	Medicine use What is obviously important here is the effect of drugs on the pregnant woman and the unborn child. Attention should also be paid to the effect on lactation and the effects in the neonatal period. In cases of doubt, consultation should take place. Note: information is available from the NIAD (030-2971100) and from the teratology center of the RIVM (030-2742017).	A/ B
4.20	Use of hard drugs (heroin, methadone, cocaine, XTC etc.) The severity of the addiction to hard drugs is important here and their effects during pregnancy and birth and in the puerperium, particularly for the neonate.	C
4.21	Alcohol abuse This involves the fetal alcohol syndrome. Obviously the long-term involvement of the pediatrician can be necessary during follow up.	C
4.22	Psychiatric disorders (neuroses/psychoses) The severity of the psychiatric problems and the opinion of the physician in charge of treatment are important.	A/ C
4.24	Hyperemesis gravidarum	C

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	Referral to secondary care is necessary for treatment of this condition. After recovery the pregnancy and birth can take place at primary care level.	
4.24	Ectopic pregnancy	C
4.25	Antenatal diagnostics Attention should be given to the presence of a risk for congenital deformities. If no deformities can be found, then further care can take place at primary level. In cases of an age-related indication, direct referral from primary care level to a genetic center can take place.	C
4.26	(Suspected) fetal deformities	B
4.27	Pre-term rupture of membranes (<37 weeks amenorrhoea)	C
4.28	Diabetes Mellitus (incl. pregnancy diabetes)	C
4.29	Pregnancy induced hypertension This refers to hypertension (according to the ISSHP definition, see 1.16) in the second half of pregnancy in a previously normotensive woman. Distinction is drawn between diastolic blood pressure up to 95 mm and blood pressure starting at 95 mm. At a diastolic pressure between 90 and 95 mm, a pregnant woman should receive extra care, from 95 mm upwards, she should be referred to secondary level care.	A/ C
4.30	Pre-eclampsia, super-imposed pre-eclampsia, HELLP-syndrome Pre-eclampsia is a combination of pregnancy induced hypertension and proteinuria. The latter is defined by an albustix ++ in a urine sample or by a total protein excretion of 30 mg or more during a period of 24 hours. A super-imposed pre-eclampsia exists when there is 'de novo' proteinuria during a pregnancy in a patient with pre-existing hypertension. The HELLP-syndrome is characterised by the combination of haemolysis, liver function disorder and a decrease in the number of platelets.	C
4.31	Blood group incompatibility	C
4.32	Thrombosis	C
4.33	Coagulation disorders	C
4.34	Recurring blood loss prior to 16 weeks	B
4.35	Blood loss after 16 weeks After the blood loss has stopped, care can take place at primary care level if no incriminating causes were found.	C
4.36	Placental abruption	C
4.37	(Evaluation of) negative size-date discrepancy A negative size-date discrepancy exists if the growth of the uterus remains 2 to 4 weeks behind the normal size for the duration of the pregnancy.	B

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4.38	(Evaluation of) positive size-date discrepancy	B
4.39	Post-term pregnancy This refers to amenorrhoea lasting longer than 294 days.	C
4.40	Threat of or actual pre-term birth As soon as there is no longer a threat of pre-term birth, care during the pregnancy and birth can be continued at primary care level.	B
4.41	Insufficient cervix Once the pregnancy has lasted 37 weeks, further care can take place at primary care level.	C
4.42	Symphysis pubis dysfunction (pelvic instability) This refers to complaints that started during the present pregnancy	A
4.43	Multiple pregnancy	C
4.44	Abnormal presentation at full term (including breech presentation)	C
4.45	Failure of head to engage at full term If at full term there is a suspected cephalo-pelvic disproportion, placenta praevia or comparable pathology, consultation is indicated.	B
4.46	No prior prenatal care (full term) Attention should be paid to the home situation. The lack of prenatal care can suggest psychosocial problems. This can lead to further consultation and a hospital delivery.	A
4.47	Baby up for adoption The prospective adoption often goes hand-in-hand with psychosocial problems. This can lead to further consultation and a hospital delivery.	A
4.48	Dead fetus If the mother prefers to give birth at home, the care she receives should be the same as if the birth were to take place in a hospital. Attention should be paid to postmortem examination study and evaluation according to protocol.	C
4.49	Obstetrically relevant fibroids (myoma) Depending on the anatomical proportions, the possibility of a disturbance in the progress of pregnancy or birth should be taken into account.	B

5. Occurring during birth

For the C-category in this section, when one of the items mentioned below occurs, an attempt should still be made to achieve an optimal condition for further intrapartum care, whilst referral to secondary care level may be urgent, depending on the situation. When referring from the home situation, the risk of transporting the woman also needs to be included in the considerations.

5.1	Abnormal presentation of the child What counts here is abnormal presentation and not abnormal position.	B
5.2	Signs of fetal distress It is important that fetal distress can be expressed in various ways (fetal heart rate, meconium staining in the amniotic fluid).	C
5.3	Intrapartum fetal death Attention should be paid to post-mortem examinations	C
5.4	Pre-labour rupture of membranes Referral should take place the morning after the membranes have been broken for 24 hours.	C
5.5	Failure to progress in the first stage of labour If the contractions are good, both regarding strength and frequency, but there is no change in the cervix or progress in dilation after the latent phase for duration of 4 hours; one can speak of a failure to progress in labour. Consultation is necessary to be able to determine further treatment based on an analysis of the possible cause.	B
5.6	Failure to progress in second stage of labour This exists where there is a lack of progress, after a maximum of one hour, in cases with full dilation, ruptured membranes, strong contractions and sufficient maternal effort.	C
5.7	Excessive bleeding during birth The degree of bleeding during birth cannot be objectively measured, but needs to be estimated. Excessive loss of blood can be a sign of a serious pathology.	C
5.8	Placental abruption	C
5.9	Umbilical cord prolapse	C
5.10	(Partial) retained placenta It is not always possible to be sure of the retention of part of the placenta. If there is reasonable cause to doubt, then referral to secondary care should take place	C
5.11	Fourth degree perineal laceration	C
5.12	Meconium stained amniotic fluid	C
5.13	Fever It is obviously important to find out the cause of the fever. In particular, the possibility of an intrauterine infection should be taken into account and the administration of antibiotics intrapartum should be considered.	C
5.14	Analgesia It is important to be aware of the effects on dilatation and respiratory depression. The use of painkillers during birth is a subject that can be covered during local discussions	B

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	with the aid of guidelines. One should attempt to achieve well-founded consensus.	
5.15	Vulva haematoma Treatment policy is determined according to the complaints intrapartum and in the early puerperium.	C
5.16	Symphyiolysis This refers to rupturing of the symphyseal rupture. It should be distinguished from pelvic instability. The added value of consultation in cases of pelvic instability has not been proven.	B
5.17	Birth with no prior prenatal care A lack of prenatal care can be a sign of psychosocial problems and in particular addiction. Intrapartum monitoring, serological screening and immunisation are of utmost importance.	C

6. Occurring during the puerperium

6.1	Puerperal fever It is important to know the underlying cause. In cases of reasonable doubt, referral should be considered.	A/C
6.2	(Threat of) eclampsia, (suspected) HELLP-syndrome	C
6.3	Thrombosis	C
6.4	Psychosis It is important to involve (non-obstetrically) the GP and the psychiatrist in treating the psychiatric disorder.	B
6.5	Postpartum haemorrhage	C
6.6	Hospitalisation of child It is obviously important here to involve (non-obstetrically) the GP and the pediatrician. The bonding between mother and child are important in the period following birth.	C

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Ontario College of Midwives Indications for Mandatory Discussion, Consultation and Transfer of Care (effective January 2015)

According to the midwifery model of care, the midwife works in partnership with the client. As a provider of primary healthcare, the midwife is fully responsible for the clinical assessment, planning and delivery of care for each client. The client remains the primary decision-maker regarding her own care, and that of her newborn.

Throughout the antepartum, intrapartum and postpartum periods, clinical situations may arise in which the midwife will need to initiate involvement of other health care providers in the care of a client or her newborn. According to the requirements of this Standard, she will:

- **Consult** with a physician, or the most appropriate available health care provider, or
- **Transfer responsibility for primary care** to a physician

Definitions

Consultation with a Physician, or other appropriate health care provider

- Consultation is an explicit request from a midwife of a physician, or other appropriate health care provider, to give advice on a plan of care and participate in the care as appropriate.
- It is the midwife's responsibility to decide when and with whom to consult and to initiate consultations.
- Consultation may result in the physician, or other health care provider, giving advice, information and/or therapy to the woman/newborn directly or recommending a plan of care and/or therapy to be carried out by the midwife.
- After consultation with a physician, the role of most responsible provider either remains with the midwife or is transferred to the consulting physician.
- Consultation may be initiated at the client's request.

Transfer of Care to a Physician

- Transfer of care occurs when the primary care responsibilities required for the appropriate care of the client fall outside of the midwife's scope of practice.
- A transfer of care may be permanent or temporary.
- When primary care is transferred from the midwife to a physician, the physician assumes full responsibility for the subsequent planning and delivery of care to the client.
- The client remains the primary decision-maker regarding her care and the care of her newborn.
- After a transfer of care has taken place the midwife shall remain involved as a member of the health care team and provide supportive care to the client within the scope of midwifery.
- If the condition for which the transfer of care was initiated is resolved, the midwife may resume primary responsibility for the care of the mother and/or newborn.

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Midwife's Responsibilities

- In all instances where another health care provider is required in the care of a midwife's client or her newborn, the midwife shall:
- Review the *Consultation and Transfer of Care Standard* with the client as part of an informed choice discussion.
- Respect the principles of informed choice, and support the client decision making process.
- Ensure that a client's decision not to pursue a consultation with another health care provider is clearly documented in the client's health record, in accord with the standards of the College of Midwives.
- Ensure that a client's decision not to follow a consultant's recommendation, once it is communicated to the midwife, is documented in the client's health record, in accord with the standards of the College of Midwives.
- Involve the other health care provider within an appropriate time frame.
- Ensure that the request for a consultation or transfer of care are both clearly articulated to the other health care provider and the client, and documented in the client's health record.[4]
- Ensure, where possible, that a consultation includes an in-person evaluation of the client or her newborn and that a consultation is initiated by phone where urgency, distance or climatic conditions make an in-person consultation impossible.
- Ensure that the subsequent plan of care, including the roles and responsibilities of the primary care providers involved, are communicated to the clinicians, and to the client and documented in the client's health record.
- Remain accountable for the care they have provided whether working collaboratively or independently.
- Throughout the course of care other indications not specifically referenced in this Standard may arise which require the involvement of other health care providers. Notwithstanding the indications listed in this Standard, midwives are expected to use their best clinical judgment supported by the highest quality available evidence and relevant guidelines, to determine when the involvement of other health care practitioners is warranted.

Indications: Initial History and Physical Examination

Consultation

- Significant current medical conditions that may affect pregnancy or are exacerbated due to pregnancy
- Significant use of drugs, alcohol or other substances with known or suspected teratogenicity or risk of associated complications
- Previous uterine surgery other than one documented low-segment cesarean section
- History of cervical cerclage
- History of more than one second-trimester spontaneous abortion
- History of three or more consecutive first-trimester spontaneous abortions
- History of more than one preterm birth, or preterm birth less than 34+ 0 weeks in most recent pregnancy
- History of more than one small for gestational age infant
- History of severe hypertension or pre-eclampsia, eclampsia or HELLP syndrome

- Previous neonatal mortality or stillbirth which likely impacts current pregnancy

Transfer of care

- Cardiac disease
- Renal disease
- Insulin-dependent diabetes mellitus
- HIV positive status

Indications: Prenatal Care

Consultation

- Significant mental health concerns presenting or worsening during pregnancy
- Persistent or severe anemia unresponsive to therapy
- Severe hyperemesis unresponsive to pharmacologic therapy
- Abnormal cervical cytology requiring further evaluation
- Significant non-obstetrical or obstetrical medical conditions arising during pregnancy
- Sexually transmitted infection requiring treatment
- Gestational diabetes unresponsive to dietary treatment
- Urinary tract infection unresponsive to pharmacologic therapy
- Persistent vaginal bleeding other than uncomplicated spontaneous abortion less than 14+0 weeks
- Fetal anomaly that may require immediate postpartum management
- Evidence of intrauterine growth restriction
- Oligohydramnios or polyhydramnios
- Twin pregnancy
- Isoimmunization
- Persistent thrombocytopenia
- Thrombophlebitis or suspected thromboembolism
- Gestational hypertension
- Vasa previa
- Asymptomatic placenta previa persistent into third trimester
- Presentation other than cephalic, unresponsive to therapy, at or near 38+0 weeks
- Intrauterine fetal demise
- Evidence of uteroplacental insufficiency
- Uterine malformation or significant fibroids with potential impact on pregnancy

Transfer of care

- Molar pregnancy
- Multiple pregnancy (other than twins)
- Severe hypertension or pre-eclampsia, eclampsia or HELLP syndrome
- Placental abruption or symptomatic previa
- Cardiac or renal disease with failure
- Gestational diabetes requiring pharmacologic treatment

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Indications: Labor, Birth, and Immediate Post-Partum

Consultation

- Preterm prelabour rupture of membranes (PPROM) between 34 +0 and 36 +6 weeks
- Twin pregnancy
- Breech or other malpresentation with potential to be delivered vaginally
- Hypertension presenting during the course of labour
- Abnormal fetal heart rate pattern
- Suspected intra amniotic infection
- Labor dystocia unresponsive to therapy
- Intrauterine fetal demise
- Retained placenta
- Third or fourth degree laceration
- Periurethral laceration requiring repair

Transfer of care

- Active genital herpes at time of labour or rupture of membranes
- HIV positive status
- Preterm labour or PPROM less than 34 +0 weeks
- Fetal presentation that cannot be delivered vaginally
- Multiple pregnancy (other than twins)
- Prolapsed or presenting cord
- Placental abruption, placenta previa or vasa previa
- Severe hypertension or pre-eclampsia, eclampsia or HELLP syndrome
- Suspected embolus
- Uterine rupture
- Uterine inversion
- Hemorrhage unresponsive to therapy

Indications: Post-partum (Maternal)

Consultation

- Breast or urinary tract infection unresponsive to pharmacologic therapy
- Suspected endometritis
- Abdominal or perineal wound infection unresponsive to non-pharmacologic treatment
- Persistent or new onset hypertension
- Significant post-anesthesia complication
- Thrombophlebitis or suspected thromboembolism
- Significant mental health concerns including postpartum depression and signs or symptoms of postpartum psychosis
- Persistent bladder or rectal dysfunction
- Secondary postpartum hemorrhage
- Uterine prolapse
- Abnormal cervical cytology requiring treatment

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Transfer of care

- Postpartum eclampsia
- Postpartum psychosis

Indications: Post-partum (Infant)

Consultation

- 34 +0 to 36 +6 weeks gestational age
- Suspected neonatal infection
- In utero exposure to significant drugs, alcohol, or other substances with known or suspected teratogenicity or other associated complications
- Findings on prenatal ultrasound that warrant postpartum follow up
- Prolonged PPV or significant resuscitation
- Failure to pass urine or meconium within 36 hours of birth
- Suspected clinical dehydration
- Feeding difficulties not resolved with usual midwifery care
- Significant weight loss unresponsive to interventions or adaptation in feeding plan
- Failure to regain birth weight by three weeks of age
- Infant at or less than 5th percentile in weight for gestational age
- Single umbilical artery not consulted for prenatally
- Congenital anomalies or suspected syndromes
- Worsening cephalhematoma
- Excessive bruising, abrasions, unusual pigmentation and/or lesions
- Significant birth trauma
- Abnormal heart rate, pattern or significant murmur
- Hypoglycemia unresponsive to initial treatment
- Hyperglycemia
- Suspected neurological abnormality
- Persistent respiratory distress
- Persistent cyanosis or pallor
- Fever, hypothermia or temperature instability
- Vomiting or diarrhea
- Evidence of localized or systemic infection
- Hyperbilirubinemia requiring medical treatment or any jaundice within the first 24 hours
- Suspected seizure activity

Transfer of care

- Major congenital anomaly requiring immediate intervention

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College of Midwives of British Columbia: Indications for Mandatory Discussion, Consultation and Transfer of Care

As a primary caregiver, the midwife is fully responsible for decision-making, together with the client. The midwife is responsible for writing orders and carrying them out or delegating them

to an appropriate regulated health professional in accordance with the standards of the College of Midwives.

The midwife discusses care of a client, consults, and/or transfers primary care responsibility according to the *Indications for Discussion, Consultation and Transfer of Care.* The responsibility to consult with a family physician/general practitioner, obstetrician, pediatrician, other specialist physician or a nurse practitioner lies with the midwife. It is also the midwife's responsibility to initiate a consultation within an appropriate time period after detecting an indication for consultation. The severity of the condition and the availability of a physician will influence these decisions.

The College of Midwives expects members to use their professional judgment in making decisions to consult or transfer care. The following list is not exhaustive. Other circumstances may arise where the midwife believes consultation or transfer of care is necessary.

The informed choice agreement between the midwife and client should outline the extent of midwifery care, so that the client is aware of the scope and limitations of midwifery care. The midwife should review the *Indications for Discussion, Consultation and Transfer of Care* with the client.

Definitions

Discussion with a midwife, a physician, or nurse practitioner

It is the midwife's responsibility to initiate a discussion with, or provide information to, another midwife or a physician in order to create an appropriate plan of care. It is also expected that the midwife will conduct regularly scheduled reviews of client charts with her colleagues to assist in planning care. Discussion should be documented by the midwife in the client record.

Consultation with a physician or a nurse practitioner

It is the midwife's responsibility to initiate a consultation in accordance with the standards of the College and to communicate clearly to the consultant that she is seeking a consultation and why. In requesting a consultation, a midwife uses her professional knowledge of the client and requests the opinion of a physician or nurse practitioner qualified to give advice in the area of clinical concern. A midwife may also seek a consultation when another opinion is requested by the client. The midwife must document each consultation in the client record in accordance with the standards of the College of Midwives.

The midwife should expect the consultant to address the problem described in the consultation request, conduct an in-person assessment(s) of the client, and promptly communicate findings and recommendations to the client and to the referring midwife. Discussion will then normally occur between the midwife and the consultant regarding the future plan of care for the client.

Where urgency, distance or climatic conditions do not allow the client to see a physician or nurse practitioner for an in-person consultation visit, the midwife should seek advice from the consultant by

phone or other similar means. The consultant may use alternative means of communication (e.g., via telehealth) to assess the client as available and appropriate. The midwife should document such requests for advice in client records, in accordance with the standards of the College of Midwives, and discuss the advice received with the client.

A consultation can involve the physician or nurse practitioner providing advice and information, and/or providing therapy to the woman/newborn, or recommending therapy for the woman/newborn to the midwife to provide within her scope of practice.

After consultation with a physician or nurse practitioner, primary care of the client and responsibility for decision-making, with the agreement of the consultant and the informed consent of the client, may:

- Continue with the midwife;
- Be shared between the midwife, nurse practitioner and/or physician; or
- Be transferred to the physician.

Once a consultation has taken place and the consultant's findings, opinions and recommendations have been communicated to the client and the midwife, the midwife must discuss the consultant's recommendations with the client and ensure that the client understands which health professional will have responsibility for primary care.

Shared primary care

In a shared care arrangement the consultant may be involved in, and responsible for, a discrete area of the client's care, with the midwife maintaining overall responsibility within her scope of practice, or vice versa. Areas of involvement in client care and the plan for communication between care providers must be clearly agreed upon and documented by the midwife and the consultant.

It is recommended that one health professional take responsibility for coordinating the client's care. This arrangement should be clearly communicated to the client and documented in the records. Responsibility can be transferred temporarily from one health professional to another, or be shared between health professionals, according to the client's best interests and optimal care. Transfer of care or an arrangement for sharing care should be discussed with the client, agreed to between the midwife and the consultant(s), and documented in the client record.

Shared primary care arrangements may vary depending on community and on the experience and comfort levels of the care providers involved. Midwives who gain more skills and abilities and experience over time may be able to manage more complex care within their scope of practice in collaboration with their physician colleagues.

Transfer to a physician for primary care

When primary care is transferred permanently or temporarily from the midwife to a physician, the physician assumes full responsibility for subsequent decision-making, together with the client. When primary care is transferred to a physician, the midwife may continue to provide supportive care, and any care within her scope of practice that is agreed to by the physician who is in the role of most responsible care provider, and that has the consent of the client.

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Indications: Initial History and Physical Examination

Discussion

- Adverse socio-economic conditions
- Age less than 17 years or over 40 years
- Cigarette smoking
- Grand multipara (5 or more previous births)
- History of infant over 4,500 g
- History of one late miscarriage (after 14 weeks) or pre-term birth
- History of one low-birth-weight infant
- History of serious psychological problems
- Less than 12 months from last delivery to present due date
- Obesity
- Poor nutrition
  Previous antepartum hemorrhage
- Previous postpartum hemorrhage
- One documented previous low-segment cesarean section
- History of hypertensive disorders of pregnancy
- Known uterine malformations or fibroids
- History of trauma or sexual abuse

Consultation

- Current medical conditions, for example: cardiovascular disease, pulmonary disease, endocrine disorders, hepatic disease, neurologic disorders, severe gastrointestinal disease
- Family history of genetic disorders, hereditary disease or significant congenital anomalies
- History of cervical cerclage or incompetent cervix
- History of repeated spontaneous abortions
- History of more than one late miscarriage or pre-term birth
- History of more than one low-birth-weight infant
- History of eclampsia
- History of significant medical illness
- Previous myomectomy, hysterotomy or cesarean section other than one
- Documented previous low-segment cesarean section
- Previous neonatal mortality or stillbirth
- Rubella during first trimester of pregnancy
- Significant use of drugs, alcohol or other toxic substances
- Age less than 14 years
- History of postpartum hemorrhage requiring transfusion

Transfer

- Any serious medical condition, for example: cardiac or renal disease with failure, or insulin-dependent diabetes mellitus

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Indications: Prenatal Care

Discussion

- Presentation other than cephalic at 4 weeks prior to due date
- No prenatal care before 28 weeks gestation
- Uncertain expected date of delivery

Consultation

- Anemia (unresponsive to therapy)
- Documented post-term pregnancy (42 completed weeks) suspected or diagnosed
- Fetal anomaly that may require physician management during or immediately after delivery
- Inappropriate uterine growth
- Medical conditions arising during prenatal care, for example: endocrine disorders, hypertension, renal disease, suspected or confirmed significant infection, including h1n18, hyperemesis
- Placenta previa without bleeding
- Polyhydramnios or oligohydramnios
- Gestational hypertension
- Isoimmunization, haemoglobinopathies, blood dyscrasia
- Serious psychological problems
- Sexually transmitted disease
- Twins
- Repeated vaginal bleeding other than transient spotting
- Presentation other than cephalic at 37 weeks
- Insulin-dependent gestational diabetes

Transfer

- Cardiac or renal disease with failure
- Multiple pregnancy (other than twins)
- Severe pre-eclampsia12 or eclampsia
- Symptomatic placental abruption

Indications: During Labor and Delivery

Discussion

- No prenatal care
- Thin, non-particulate meconium

Consultation

- Breech presentation
- Pre-term labor (34 – 36 + 6 weeks)
- Prolonged active phase
- Prolonged rupture of membranes
- Prolonged second stage
- Suspected placenta abruption and/or previa

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- Retained placenta
- Third or fourth degree tear
- Twins
- Unengaged head in active labor in primipara
- Thick or particulate meconium
- Temperature of 38°c or greater on more than one occasion

Transfer

- Active genital herpes at time of labor
- Pre-term labor (less than 34 weeks)
- Abnormal presentation (other than breech)
- Multiple pregnancy (other than twins)
- Severe pre-eclampsia or eclampsia
- Prolapsed cord
- Placenta abruption and/or previa
- Severe hypertension
- Abnormal fetal heart rate patterns unresponsive to therapy
- Uterine rupture
- Uterine inversion
- Hemorrhage unresponsive to therapy
- Obstetric shock

Indications: Post-partum (Maternal)

Consultation

- Breast infection unresponsive to therapy
- Wound infection
- Uterine infection
- Signs of urinary tract infection unresponsive to therapy
- Temperature over 38°c on more than one occasion
- Persistent hypertension
- Serious psychological problems

Transfer

- Hemorrhage unresponsive to therapy
- Eclampsia
- Thrombophlebitis or thromboembolism
- Uterine prolapse

Indications: Post-partum (Infant)

Discussion

- Feeding problems
- Excessive moulding

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- Cephalohaematoma

Consultation

- Suspicion of or significant risk of neonatal infection
- 34 to 36 +6 weeks gestational age
- Infant less than 2,500 g
- Less than 3 vessels in umbilical cord
- Abnormal findings on physical exam
- Excessive bruising, abrasions, unusual pigmentation and/or lesions
- Birth injury requiring investigation
- Congenital abnormalities, for example: cleft lip or palate, developmental dysplasia of the hip, ambiguous genitalia
- Abnormal heart rate or pattern
- Persistent poor suck, hypotonia or abnormal cry
- Persistent abnormal respiratory rate and/or pattern
- Persistent cyanosis, pallor or jitteriness
- Jaundice in first 24 hours
- Failure to pass urine or meconium within 24 hours of birth
- Suspected pathological jaundice after 24 hours
- Temperature less than 36°C unresponsive to therapy
- Temperature of 38°C or more unresponsive to therapy
- Vomiting or diarrhea
- Infection of umbilical stump site
- Significant weight loss (more than 10% of body weight)
- Failure to regain birth weight in 3 weeks
- Failure to thrive

Transfer

- Apgar score lower than 7 at 10 minutes
- Suspected seizure activity
- Significant congenital anomaly requiring immediate medical intervention, for example: omphalocele, myelomeningocele
- Temperature instability

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APPENDIX B. GRADE ELEMENT DESCRIPTIONS

Element	Description
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Resource allocation	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted

Strong recommendation

In Favor: The subcommittee is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Against: The subcommittee is confident that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Weak recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Quality or strength of evidence rating across studies for the treatment/outcome[18]

High: The subcommittee is very confident that the true effect lies close to that of the estimate of the effect. Typical sets of studies are RCTs with few or no limitations and the estimate of effect is likely stable.

Moderate: The subcommittee is moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.

Low: The subcommittee's confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

Very low: The subcommittee has very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

[18] Includes risk of bias, precision, directness, consistency and publication bias

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APPENDIX C. METHODOLOGY, NEW EVIDENCE SEARCH, AND SUMMARY PROCESS DESCRIPTION

1) Conduct MEDLINE® search to update and expand on trusted source review conducted in 2014 at initiation of the topic for HERC. Search strategy attached below was developed by an Research Associate for the Center for Evidence-based Policy (Center) and an experienced health care librarian at Oregon Health & Science University with extensive experience working on systematic reviews (SRs). The search was conducted with the following parameters:
    a. 10-year search (January 2005-April 2015) to capture sources that Wax 2010 SR, which was included from initial trusted source search, may have missed or excluded. Search also limited to 10-year time frame to avoid including studies that were conducted in time periods that now would be considered to be outdated obstetric practice.
    b. MEDLINE® search for both SRs (with or without meta-analyses), randomized trials and cohort studies
    c. Broad search terms encompassing out-of-hospital birth, home birth, and birthing center locations with a variety of outcomes, both in the U.S. and abroad
    d. Review of included study reference lists and public comments to the HERC to identify any additional studies

2) Dual review by Center epidemiology staff for inclusions & exclusions

    a. Inclusion criteria:
        i. Population-based study of relevant patient populations in countries with developed health care systems similar to the U.S.;
        ii. N > 1000 in OOH birth group;
        iii. Exclusion or control or reporting of patients deemed a priori high-risk by HERC (multiple birth, breech, prior Cesarean birth, non-vertex);
        iv. Inclusion and analysis by planned birth setting;
        v. Reporting of relevant maternal or fetal/neonatal outcomes;
        vi. Abstractable data; or
        vii. Not a narrative review, opinion, comment or letter to the editor.

3) Evidence summary and addendum to HERC Coverage Guidance document based on additional studies meeting inclusion criteria, with quality rating of evidence

4) EbGS to update coverage guidance language, as appropriate, based on updated evidence search and additional discussion

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Table C1. MEDLINE® Search Strategy

Database: Ovid MEDLINE® without Revisions <1996 to April Week 3 2015>

1	exp Home Childbirth/	2152
2	((plan or plans or plann$) adj3 (birth$ or born or deliver$) adj7 (house$ or home or homes or ((away or outsid$) adj3 (hospital$ or facilit$)))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	191
3	exp Birthing Centers/	567
4	(birth$ adj center$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	831
5	(birth$ adj2 setting$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	235
6	(midwi$ adj3 (home or homes or hous$)).mp.	186
7	1 or 2 or 3 or 4 or 5 or 6	3216
8	exp Mortality/	291819
9	mo.fs.	436286
10	advers$.mp.	327767
11	exp "Outcome and Process Assessment (Health Care)"/	765349
12	exp Economics/	503207
13	ec.fs.	345974
14	exp Pregnancy Complications/	349245
15	exp Risk/	874947
16	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	2976033
17	7 and 16	1360
18	limit 17 to yr="2005 -Current"	721
19	limit 18 to english language	677
20	limit 19 to journal article	593

21	limit 19 to (comment or editorial or letter or news)	92
22	19 not 21	585
23	20 or 22	596

Center staff excluded 558 citations of the 596 identified by the MEDLINE® search based on not meeting inclusion criteria for this review and reviewed 38 full text articles for possible final inclusion.

During full text review of the MEDLINE® search results, two studies were excluded as duplicates, four studies did not have abstractable data, two were excluded because of country setting and five on the basis of the included population.

An additional 20 sources were identified from references in included studies, a final MEDLINE® update conducted on May 20, 2015 (21 citations were identified; two were selected for full text review, and one was included), and/or from public comment and testimony to the HERC. Twelve of these were peer reviewed publications. Of these 12, three were identified in the initial MEDLINE® search on April 22, 2015 and two were identified in the final MEDLINE® search on May 20, 2015. The remaining nine articles were not specifically on the topic of OOH birth and were submitted as part of public comment related to risk criteria.

After full text review of a total of 40 studies, 15 met inclusion criteria and were abstracted into Table C1.

The authors of two studies (Cheyney, 2014; Janssen, 2009) which had not reported all perinatal mortality outcomes by parity, and which were relevant to Oregon, were contacted for additional data.

References Suggested Through Public Comment And Testimony Process

Suggested references that were also identified in MEDLINE® search and are included in evidence summary

Birthplace in England Collaborative Group; Brocklehurst, P., Hardy, P., Hollowell, J., Linsell, L., Macfarlane, A., McCourt, C. … Stewart, M. (2011). Perinatal and maternal outcomes by planned place of birth for healthy women with low risk pregnancies: The Birthplace in England national prospective cohort study. *British Medical Journal, 343*, d7400. http://www.bmj.com/content/343/bmj.d7400.full.pdf+html

Cheyney, M., Bovbjerg, M., Everson, C., Gordon, W., Hannibal , D., & Verdam, S. (2014). Outcomes of care for 16,924 planned home births in the United States: the Midwives Alliance of North America Statistics Project, 2004-2009. *Journal of Midwifery & Women's Health, 59*(1), 17-27. http://onlinelibrary.wiley.com/doi/10.1111/jmwh.12172/epdf

Stapleton, S. R., Osborne, C., & Illuzzi, J. (2013). Outcomes of care in birth centers: Demonstration of a durable model. *Journal of Midwifery & Women's Health, 58*(1), 3-14. http://onlinelibrary.wiley.com/doi/10.1111/jmwh.12003/epdf

Suggested references which were not included in evidence summary because they did not meet inclusion criteria (but which were included in public comment disposition)

American Congress of Obstetricians and Gynecologists (ACOG). (2013, November 14). *Ob-gyns issue task force report on hypertension in pregnancy: Preeclampsia diagnosis no longer requires presence of proteinuria*. http://www.acog.org/About-ACOG/News-Room/News-Releases/2013/Ob-Gyns-Issue-Task-Force-Report-on-Hypertension-in-Pregnancy

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Table C2: Evidence Table for Out-of-Hospital Birth Studies, New Search

Citation	Study Description	Fetal & Neonatal Outcomes#, +	Maternal Outcomes#	Study Quality* (GRADE) Comments
Studies with Outcomes Reported by Parity				
U.S.-based Studies				
Cheng, 2013	U.S. Retrospective cohort study U.S. birth certificates from 27 states using 2003 modification noting planned and actual place of birth. N=12,039 planned home births of 2,081,753 births meeting study criteria, out of 4,247,694 total U.S. births in 2008. Exclusion criteria included <37, >=43 wk EGA; breech; multifetal; birth at freestanding birth cntr; accidental home birth; unclear planned location of birth. Included multips with history of prior CS. 21.0% Nulliparas in home birth group. Significant differences (p<0.001) among planned home and hospital groups for all reported characteristics,	Results below are for planned site of birth and also by attendant, abbreviations as follows: Hospital (Hosp) Home CNM-CM (Home-CNM) Home-Other Midwife (Home-OMW) **Primary outcome--5 min Apgar <4** [# (%)], by parity, by site/provider Nulliparas Hosp: 2843 (0.34%) Home-CNM: 3 (0.42%) Home-OMW: 5 (0.37%) Multiparas Hosp: 2185 (0.18%) Home-CNM: 3 (0.12%) Home-OMW: 12 (0.25%) adjOR 5 min Apgar<4 [crudeOR not reported, adjOR adjusted for parity, maternal age, race/ethnicity,	CS not reported For mode of delivery, only **operative vaginal delivery** was reported: adjOR (planned home v. hospital) 0.12 (0.08-0.42) (Very small data cell for planned home birth where only 10 cases reported among 12,039 births) Other maternal outcomes reported: Induction of Labor Augmentation of Labor Antibiotic use in labor	**Very low (OOO+)** Sample included fewer than 50% of U.S. births during 2008. No linkage to fetal/neonatal death files for mortality outcomes. All outcomes are surrogates/short term outcomes with most relevant outcome being 5 min Apgar <4 which is associated with poor perinatal outcome. Two studies were cited with 5 min Apgar score of 0-3 associated with neonatal mortality rate of 20-21/1000 among term births. Some birth certificate items very poor sensitivity. Large state variation in 2003 revised birth certificate sensitivity compared to medical records has also been reported for some items (such as NICU admission, neonatal assisted ventilation, antibiotics for suspected neonatal sepsis and meconium staining) by the National Center for Health Statistics. Planned place of birth a relatively new data item on birth certificates and no validation offered for this key variable. The 2003 birth certificate revision asks “Place where birth

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Citation	Study Description	Fetal & Neonatal Outcomes#, +	Maternal Outcomes#	Study Quality* (GRADE) Comments
	including parity, age, race/ethnicity, marital status, years of education, month of initiation of prenatal care and gestational age a birth. Multivariable logistic regression model adjusted for parity, maternal age, race/ethnicity, educational attainment, marital status, EGA at delivery, cigarette use during pregnancy, prenatal visits, medical conditions (prepregnancy htn or DM, gestational htn or GDM and/or preeclampsia, eclampsia. Total Nulliparas, N=840,641 Total Multiparas, N=1,227,272	education, GA, number of PN care visits, cigarette smoking, medical/obstetric conditions] *Home-CNM v. Hospital* Nullip adjOR 0.47 (0.07-3.38) Multip adjOR 0.83 (0.27-2.6) *Home-OMW v. Hospital* Nullip adjOR 1.34 (0.55-3.22) Multip adjOR 1.84 (1.04-3.26) *Other outcomes reported* 5 min Apgar <7 Ventilator support >6 hrs NICU admission Neonatal seizures (very small cells—2 each among nullips and multips at home with other midwife and 1 among multip at home with CNM)		occurred (Check one)" and gives options of Hospital, Freestanding birthing center, Home Birth, Clinic/Doctor's Office, or Other (Specify). Only the home birth selection asks the additional question of "Planned to delivery at home?" (2003 Revisions of the U.S. Standard Certificates of Live Birth: http://www.cdc.gov/nchs/data/dvs/birth11-03final-ACC.pdf) No way to attribute intention to treat analysis factors (planned home vs. transfer to hospital for actual place of birth). Transfer from hospital to home much less likely than home to hospital may give positive bias to home birth. Large sample size with use of U.S. data and analysis by parity and type of OOH birth attendant. adjOR may be overadjusted for risk factors and not present adequate impression of average case, but useful for assessment of lowest risk population estimate. Despite adjustment, likely residual confounding based on factors not captured on birth certificate.
Cheyney, 2014	U.S. Prospective, non-comparative cohort Data collected using MANA (Midwives Alliance of North America) web-based tool	**Perinatal mortality [#, rate per 1000, (95% CI)]** Overall PM (non-anomalous), all parities 35/16,980 or 2.06/1000	**CS birth** 887/16,984 (5.2%) Other maternal outcomes reported:	**Low (OO++)** Largest study of home births, primarily attended by CPMs, in the U.S.

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Citation	Study Description	Fetal & Neonatal Outcomes#, +	Maternal Outcomes#	Study Quality* (GRADE) Comments
	(MANA Stats 2.0), 2004-2009 20-30% of active CPMs in North American participated (n=432), with ~95% of women consenting to participate. Over 79% of birth attendants were CPMs, with other types including CNMs, naturopaths, non-licensed midwives Prospective entry of subjects into database, usually early in pregnancy, before outcomes of interest known. Database variables cover first prenatal visit through 6 wks postpartum. Multiple data reviews after entry. Quality of data accuracy tested previously and found to be high. Final sample size, N=16,924 (Total dataset N=24,848. Excluded women transferred to care prior to labor, planned birth location other than home, women living outside the U.S.)	*By time of death* Intrapartum: 22/16,980 [1.30 (0.75-1.84)/1000] Early neonatal: 7/16,950 [0.41 (0.11-0.72)/1000] Late neonatal: 6/16,942 [0.35 (0.07-0.64)/1000] Total intrapartum mortality when higher-risk women removed from sample (multiple gestations, breech, TOLAC, GDM, preeclampsia): 0.85/1000 (95% CI 0.39-1.31) Intrapartum: 11/3771 [2.92 (1.20-4.64)] Early neonatal: 1/3757 [0.41 (0.11-0.72)] Late neonatal: 6/16,942 [0.35 (0.07-0.64)] Primiparous v. multiparous, intrapartum death 2.92/1000 v. 0.84/1000 (p<0.01) Primiparous v. multiparous, without risk factors 2.77/1000 v. 0.30/1000 [Author contacted for additional information since many perinatal deaths were associated with risk conditions that might preclude home birth. For primiparous women at low risk (with a non-breech presentation, no	Intrapartum transfer (and if transferred, use of epidural, oxytocin augmentation) Postpartum maternal transfer SVD, OVD Primary CS TOLAC Breech presentation	Prospective data collection with outcomes reported by parity. Good attention to data quality with prior validation study published. Not possible to assemble a comparable comparative group of CPM attended hospital births, but there were birth center births which were excluded from this sample (n=3895) and which may be reported in the future. Some additional data on nulliparity and perinatal mortality obtained from first author—see neonatal outcomes. Additional papers are in process or press from this dataset.

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Citation	Study Description	Fetal & Neonatal Outcomes#, +	Maternal Outcomes#	Study Quality* (GRADE) Comments
	Nulliparas, 22.3% of sample	gestational diabetes and no preeclampsia) there were a total of 10 perinatal deaths (8 intrapartum, 1 early neonatal, and 1 late neonatal), for PM rates of 2.21/1000, 0.28/1000, and 0.28/1000, or a total low risk primiparous PM rate of 2.77/1000] # (out of total of 35) Perinatal deaths, by risk factor Breech: 5 TOLAC: 5 Multiple gestation: 1 GDM: 2 Preeclampsia: 1 Intrapartum fetal death rate by risk factor *Breech* 13.51/1000 v. 1.09/1000 vertex (p<0.01) *TOLAC* 2.85/1000 v. 0.66/1000 for multiparas without h/o prior CS (p=0.05) Other fetal/neonatal outcomes reported: Breech presentation (early and late neonatal death) GA (pre- v. post-term) Low BW, Macrosomia		

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Citation	Study Description	Fetal & Neonatal Outcomes#, +	Maternal Outcomes#	Study Quality* (GRADE) Comments
		Neonatal transfer NICU admission		
Non-U.S.-based Studies				
Birthplace, 2011	England Prospective, comparative cohort Collected all planned home (home), freestanding midwifery unit (FMU), and alongside midwifery unit (AMU) births, and a stratified random sample of births in obstetric units (OU). Data from all NHS trusts providing home birth services between April 2008 and April 2010. Composite primary outcome used in study was combination of stillbirth after the start of care in labor, early neonatal death, neonatal encephalopathy, meconium aspiration syndrome, brachial plexus injury, fractured humerus, and fractured clavicle.	**Primary composite outcome (CO)** (stillbirth after the start of care in labor, early neonatal death, neonatal encephalopathy, meconium aspiration syndrome, brachial plexus injury, fractured humerus, and fractured clavicle for women with low risk status) Organization of presentation of CO outcome below: Incidence of events/1000 crudeOR (95% CI) weighted for duration of unit's participation in study, probability of being sampled, and clustering. adjOR adjusted for maternal age, ethnicity, understanding of English, marital/partner status, BMI, deprivation score, prior pregnancies, GA. Referent group for crudeOR and adjOR calculations are OU group. Overall CO incidence, all parities Home 4.2 (3.2-5.4) FMU 3.5 (2.5-4.9) AMU 3.6 (2.6-5.9) OU 4.4 (3.2-5.9)	**Intrapartum Cesarean Section** (events/1000) for women with low risk status Overall CS incidence (all parities) 9.9 (8.4-11.5) By planned location Home 2.8 (2.3-3.4) FMU 3.5 (2.8-4.2) AMU 4.4 (3.5-5.5) OU 11.1 (9.5-13.0) Crude and adjORs for Cesarean birth compared to referent OU category *crudeOR* Home 0.23 (0.17-0.30) FMU 0.28 (0.21-0.37) AMU 0.37 (0.28-0.49) *adjOR* Home 0.31 (0.23-0.41)	**Very Low (OOO+)** High quality, large, population-based prospective study with robust attention to data quality, design, conduct and appropriate statistical analysis. Study formed basis for 2014 NICE guideline recommendations on planned place of birth. English NHS health system, training, practice patterns, regulation of midwives and other professionals are different from U.S. systems, and may not be applicable to U.S. setting. Supplementary tables (online with study available at: http://www.bmj.com/content/343/bmj.d7400/related) Supplementary tables have event counts for stillbirth and neonatal death at 0-7d. for low risk women. These are secondary analyses and were not presented in main paper because number of events was small

Citation	Study Description	Fetal & Neonatal Outcomes#, +	Maternal Outcomes#	Study Quality* (GRADE) Comments
		crudeOR Home 0.96 (0.65—1.42) FMU 0.82 (0.52-1.28) AMU 0.84 (0.54-1.30) *adjOR* Home 1.16 (0.76-1.77) FMU 0.92 (0.58-1.46) AMU 0.92 (0.60-1.39) Nulliparas Home 9.3 (6.5-13.1) FMU 4.5 (2.8-7.1) AMU 4.7 (3.1-7.2) OU 5.3 (3.9-7.3) *crudeOR* Home 1.76 (1.10-2.82) FMU 0.85 (0.49-1.48) AMU 0.90 (0.53-1.54) *adjOR* Home 1.75 (1.07-2.86) FMU 0.91 (0.52-1.80) AMU 0.96 (0.58-1.61)	FMU 0.32 (0.24-0.42) AMU 0.39 (0.29-0.53) Other outcomes reported: Spontaneous vertex birth Vaginal breech birth Ventouse delivery Forceps delivery 3rd/4th degree perineal trauma Blood transfusion Admission to higher level of care Syntocinon augmentation Immersion in water for pain relief Epidural or spinal analgesia General anesthetic No active management of 3rd stage Episiotomy Transfer during labor Transfer immediately after birth	(total of 18 cases of stillbirth/early neonatal death among nullips and 14 among multips) and not statistically stable. The incidence figures (expressed as # (95% CI)/1000) below should be treated with caution: **Stillbirth** Nulliparas Home 0.9 (0.2-3.3) FMU 0.3 (0.0-3.5) AMU 0.1 (0.0-1.6) OU 0.1 (0.0-1.5) Multiparas Home 0.1 (0.0-0.9) FMU 0.5 (0.1-2.2) AMU 0 events OU 0.2 (0.0-1.2) **Early neonatal death (within 7d)** Nulliparas Home 0.4 (0.1-2.4) FMU 0.5 (0.1-1.7) AMU 0.1 (0.0-1.7) OU 0.4 (0.1-1.3)

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Citation	Study Description	Fetal & Neonatal Outcomes#, +	Maternal Outcomes#	Study Quality* (GRADE) Comments
		Multiparas Home 2.3 (1.6-3.2) FMU 2.7 (1.6-4.6) AMU 2.4 (1.4-4.3) OU 3.3 (2.2-5.0) *crudeOR* Home 0.70 (0.40-1.21) FMU 0.86 (0.44-1.69) AMU 0.77 (0.38-1.57) *adjOR* Home 0.72 (0.41-1.27) FMU 0.91 (0.46-1.80) AMU 0.81 (0.40-1.62) Overall CO incidence, all parities, women without complicating conditions at start of labor (prolonged ROM >18h., meconium stained fluid, proteinuria >=1+, hypertension, abnormal vaginal bleeding, non-cephalic presentation, abnormal fetal heart rate, other-unspecified) Home 4.0 (3.0-5.3) FMU 3.2 (2.3-4.6) AMU 3.4 (2.4-4.9) OU 3.1 (2.2-4.2)		Multiparas Home 0.3 (0.1-1.3) FMU 0.3 (0.1-2.2) AMU 0.1 (0.0-1.4) OU 0.1 (0.0-1.8)

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Citation	Study Description	Fetal & Neonatal Outcomes#, +	Maternal Outcomes#	Study Quality* (GRADE) Comments
		crudeOR Home 1.34 (0.88-2.05) FMU 1.11 (0.69-1.77) AMU 1.19 (0.74-1.91) *adjOR* Home 1.59 (1.01-2.52) FMU 1.22 (0.76-1.96) AMU 1.26 (0.80-1.99) Nulliparas Home 9.5 (6.6-13.7) FMU 4.5 (2.8-7.4) AMU 4.4 (2.7-7.0) OU 3.5 (2.4-5.1) *crudeOR* Home 2.81 (1.66-4.76) FMU 1.33 (0.72-2.46) AMU 1.31 (0.71-2.39) *adjOR* Home 2.80 (1.59-4.92) FMU 1.40 (0.74-2.65) AMU 1.38 (0.75-2.52)		

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Citation	Study Description	Fetal & Neonatal Outcomes#, +	Maternal Outcomes#	Study Quality* (GRADE) Comments
		Multiparas Home 2.0 (1.4-2.9) FMU 2.2 (1.3-3.8) AMU 2.5 (1.4-4.5) OU 2.6 (1.5-4.4) *crudeOR* Home 0.80 (0.41-1.54) FMU 0.90 (0.42-1.94) AMU 1.04 (0.47-2.30) *adjOR* Home 0.83 (0.44-1.58) FMU 0.97 (0.46-2.04) AMU 1.09 (0.50-2.39)		
Hutton, 2009	Ontario, Canada Retrospective matched cohort Ontario Ministry of Health Database of planned home births during 2003 to 2006. Planned home (N=6692) v. Planned hospital (N=6692)	Planned home v. planned hospital birth **Intrapartum Stillbirth** 3 v. 4 **Neonatal mortality (0-28d)** 6 v. 4 **Neonatal death (28-42d)** 0 v. 1 **Total perinatal mortality (stillbirths and**	Planned home v. planned hospital birth **Cesarean birth** 348/6692 (5.2%) v. 544/ 6692 (8.1%) RR 0.64 (0.56-0.73) **CS, by parity**	**Very Low (OOO+)** Population-based retrospective matched cohort study of midwifery care. Subjects matched on parity and for multiparous women on h/o prior CS. Matching by parity would not eliminate unmeasured confounding (systematic differences between women desiring a home v. hospital birth), but both groups were registered with midwives who have

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Citation	Study Description	Fetal & Neonatal Outcomes#, +	Maternal Outcomes#	Study Quality* (GRADE) Comments
	Nulliparas, 34.3% of both groups (groups matched on parity)	**neonatal deaths from 0-42d)** 9 v. 9 (denominator N= 6692 for each group) **Composite outcome (CO)** (perinatal/neonatal mortality or morbidity, including 5 min Apgar <4, neonatal resuscitation w/ PPV and cardiac compressions, admission to NICU w/ LOS>4d, BW<2500g) 159/6692 v. 190/6692 RR 0.84 (0.68-1.03) CO, Nulliparas v. Multiparas Home 80 (3.5%) v. 79 (1.8%) Hospital 85 (3.7%) v. 105 (2.4%) Perinatal/neonatal mortality, Nulliparas v. Multiparas Home 5 (0.2%) v. 4 (0.1%) Hospital 4 (0.2%) v. 2 (0.1%) Other outcomes reported: Breech presentation	Nulliparas 276/2293 (12%) v. 365/2298 (15.9%) Multiparas 71/4393 (1.3%) v. 179/4394 (2.6%) Other outcomes reported: Actual place of birth Ambulance transport from home during or after birth Intrapartum transfer of care Postpartum transfer of care Est. intrapartum blood loss Consultation or transfer of care for bleeding Genital tract laceration Episiotomy Induction of labor Labor augmentation Pharmaceutical pain relief	both home and hospital birth privileges which would make them more similar than a comparable group of low risk women not seeking midwifery care. Records required to be kept from entry to care, but no comment on when the "planned" place of birth was elected (early/late prenatal v. onset of labor). Records audited regularly by the College of Midwives of Ontario. Ontario midwives adhere to provincial standards for low-risk care and have education comparable to U.S. CPM or CNM. Indirectness due to non-U.S. setting as described above. Canadian practice likely most similar to U.S. compared to other non-U.S. studies, but there are differences in health care systems, as well as midwifery accreditation, licensure, and monitoring.

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Citation	Study Description	Fetal & Neonatal Outcomes#, +	Maternal Outcomes#	Study Quality* (GRADE) Comments
		Gestational age Birthweight Apgar scores Infant resuscitation NICU admission Significant congenital anomalies Infant feeding at 1 wk, 6 wks		
de Jonge, 2015	Netherlands Retrospective cohort Nationwide national database of birth registration for 10 years from 2000-2009. (This study contains 7 years of overlapping data from de Jonge, 2009.) Data from women in primary midwifery care, eligible for home birth and planning either a home or hospital birth. Planned home birth Nulliparas, n=198,515 Multiparas, n=267,526 Planned hospital birth Nulliparas, n=137,168 Multiparas, n=139,740	**Perinatal Mortality (stillbirths and neonatal deaths up to 28d)** (certain and uncertain time of death) Nulliparas Planned home birth 203/198,515 (1.02%) Planned hospital birth 150/137,168 (1.09%) Nulliparas--Home v. Hospital crudeOR 0.94 (0.76-1.16) adjOR 0.99 (0.79-1.24) (adjusted for GA, maternal age, SES, ethnicity) Multiparas Planned home birth 158/267,526 (0.59%)	No maternal outcomes reported.	**Very Low (OOO+)** Netherlands has national primary care midwifery, and home birth criteria, integrated system of home and hospital care with clear lines of responsibility for transfer and consultation. This is a high quality set of cohort studies from the Netherlands and this study represents largest database analyzed for these outcomes. Quality rating is related to the fact that these are non-randomized studies and have some indirectness as practice situation may not be applicable to U.S. settings.

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Citation	Study Description	Fetal & Neonatal Outcomes#, +	Maternal Outcomes#	Study Quality* (GRADE) Comments
		Planned hospital birth 81/139,740 (0.58%) Multiparas--Home v. Hospital crudeOR 1.02 (0.78-1.33) adjOR 1.16 (0.87-1.55) Other outcomes reported: Perinatal mortality, certain time of death Intrapartum death Neonatal death, 0-7d Neonatal death, 0-28d 5 min Apgar <4, <7 Admission to NICU Admission to NICU within 7d, 28d Severe adverse perinatal outcome (PM or NICU admission, to 28d)		
de Jonge, 2013	Netherlands Retrospective cohort Data for singleton, term (37-42 wks) births among women in primary midwifery care at onset of spontaneous labor, planning either a home or hospital birth, using national	No neonatal outcomes reported.	Planned home v. Planned hospital birth **Severe acute maternal morbidity** (composite outcome, including admission to ICU, uterine rupture, eclampsia/HELLP, transfusion of >=4 units PRBCs, or other severe morbidity as diagnosed	**Very Low (OOO+)** Netherlands has national primary care midwifery, and home birth criteria, integrated system of home and hospital care with clear lines of responsibility for transfer and consultation. Study setting may not be applicable to U.S.

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Citation	Study Description	Fetal & Neonatal Outcomes#, +	Maternal Outcomes#	Study Quality* (GRADE) Comments
	registration database, 2004-2006. National database was merged with that from the LEMMon database (database of severe maternal morbidity) to give more full information on maternal morbidity among planned home births compared to planned hospital births. Study sample size Home: N=92,333 Hospital: N=54,419 Nulliparas, n=65,227 (44.4% of sample) Multiparas, N=81,521 (55.6% of sample)		by attending clinician) [adjOR adjusted for parity, GA, maternal age, ethnicity, SES] Nulliparas crudeOR 0.74 (0.55-1.00) adjOR 0.77 (0.56-1.06) Multparas crudeOR 0.42 (0.29-0.60) adjOR 0.43 (0.29-0.63) Other outcomes reported: Admission to ICU Eclampsia or severe HELLP syndrome Transfusion of >=4 units PRBCs PPH>1000mL Manual removal of placenta	settings.
Studies with Outcomes NOT Reported by Parity				
U.S.-based Studies				
Johnson, 2005	U.S. Retrospective cohort Database of births attended by CPMs and with participating made mandatory	**Perinatal Mortality (PM)** 14/5418 (0.26%) Crude PM = 2.58/1000 adjPM (adjusted for lethal congenital anomalies [11/5415]) = 2.03/1000	**Cesarean Birth** 200/5418 (3.7%) Other outcomes reported: Timing, urgency and indication for maternal transfer to	**Very Low (OOO+)** Over 4% of CPMs did not fully participate and were excluded after agreeing to take part in study. This could have introduced selection bias or outcome assessment bias if these CPMs had poor outcomes and

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Citation	Study Description	Fetal & Neonatal Outcomes#, +	Maternal Outcomes#	Study Quality* (GRADE) Comments
	by NARM CPM recertification during 2000. 409 practicing CPMs agreed to participate in study and 18 excluded for non-participation as they decided over the year not to re-certify. 0.8% of clients declined to participate. CPM clients logged prospectively and data collected prospectively using paper forms at start of care. Care entry logs collected every 3 months and verified against data forms received. Data collected through 6 wks postpartum. Stratified random sample of CPM patients contacted as data validity check and satisfaction. Additional data collection done for cases of perinatal mortality. Final N=5418 women planning a home birth in the U.S. with a CPM. Nulliparas, 31.2% of study sample	PM among low risk women (removing breech/twins) = 1.7/1000 Intrapartum deaths = 5 (1 cord prolapse after AROM in hospital [note that this should have been classed as a neonatal death as Apgars were 1/0]; 1 cord accident [true knot], 2 complications of breech delivery, 1 subgaleal/subdural/subarachnoid hemorrhage) Neonatal deaths = 9 (3 lethal congenital anomalies; 2 with low 5 min Apgar scores died in neonatal period; 2 with high 5 min Apgar scores died suddenly at 15 and 26 hours of age; 1 post-CS for vasa previa; 1 with late onset GBS) Sample included 80 breech births (2 cases of perinatal death); and 13 twin gestations (no deaths) Other outcomes reported: Timing, urgency and indication for neonatal transfer to hospital Admission to NICU 5 min Apgar < 7 Health problems in first 6 wks	hospital Use of electronic fetal monitoring Intravenous fluids/medications Artificial rupture of membranes Epidural Induction of labor Stimulation of labor Episiotomy Forceps Vacuum extraction Health problems in first 6 wks Breastfeeding Client satisfaction	elected to stop re-certification because of this. Appears to be some potential misclassification of type of death (one early neonatal classed as an intrapartum death). Limited information available for cause/location of some perinatal deaths. Data not presented by parity. Included all births, with some at <37 wks (1.4%), some at >42 wks (6.7%). 6% of study population had maternal age >=40y. Although a PM rate adjusted for lethal congenital anomalies, and breech/twin births was provided, no information given about contribution of other high risk conditions such as these or TOLAC. However, this study likely represents average CPM practice in the U.S. in 2000, where practice is regulated differently across states and not integrated into systems of care. The PM rate is also comparable to that found in other studies.

Citation	Study Description	Fetal & Neonatal Outcomes#, +	Maternal Outcomes#	Study Quality* (GRADE) Comments
		Breastfeeding		
Stapleton, 2013	U.S. Retrospective registry-based outcomes study. Data collected for women planning birth center birth in a participating center from 2007 through 2010. Prenatal data collected prospectively using the American Association of Birth Centers (AABC) Uniform Data Set (UDS). Intrapartum, postpartum and neonatal data entered during and after birth. The UDS has been previously validated for data quality and there is ongoing audit for data quality. Seventy-nine (78%) of AABC member birth centers use the UDS registry and approximately 40% of known U.S. birth centers are members of AABC. Most AABC centers have midwifery-led care (both CNM and RM or CPM providers) in collaboration with physicians.	**Perinatal mortality** (stillbirths and neonatal death within 7d.) Fetal deaths 14/15,574 (0.09%) (7 fetal deaths occurred prior to admission in labor and 7 were intrapartum deaths. 4 intrapartum deaths occurred after auscultation of abnormal heart tones and transfer. 3 occurred to women who labored and had unexpected stillbirths.) Neonatal deaths 9/15,560 (0.058%) (2 neonatal deaths were due to known lethal congenital anomalies. 1 was due to a congenital diaphragmatic hernia not detected on 2nd trimester anatomy ultrasound scan. 2 deaths occurred among infants of women who were transferred emergently in labor for non-reassuring fetal heart tones and 1 with rupture of a velamentous cord insertion. 2 births occurred in infants who were transferred emergently after birth and had respiratory distress syndrome and 1 in an infant with hypoxic ischemic encephalopathy attributed to a prenatal insult.)	**Cesarean birth** Overall CS incidence, all parities 949/15,574 (6.1%) Other maternal outcomes reported: Intrapartum transfer Postpartum transfer Incidence and indication for emergency transfer Spontaneous vaginal birth Vaginal breech birth VBAC Assisted vaginal birth Repeat CS, with and without TOLAC	**Low (OO++)** This is the only included study of U.S. birth centers meeting inclusion criteria. It has a large sample size and collected data from a geographically diverse group of centers, including the only AABC accredited birth center in Oregon, over a 4 year period. Birth centers contributing data to the UDS registry may not be similar to those who do not support AABC membership standards and thus the findings may not be generalizable to all birth centers in the U.S. The care providers make the coding determination for intrapartum data elements such as the urgency of transfer. However, chart audit indicated that some providers coded a transport as emergent when it was not. Outcomes are not reported by parity. Although TOLAC and breech birth do not meet AABC risk criteria for accredited birth centers there were several women who experienced both in this study. It is not clear where these births took place, but all were admitted in labor to a birth center.

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Citation	Study Description	Fetal & Neonatal Outcomes#, +	Maternal Outcomes#	Study Quality* (GRADE) Comments
	Women are entered into the UDS at first prenatal visit and data is collected through a postpartum visit which generally occurs at 4 to 6 weeks postpartum. AABC eligibility for care criteria for low risk pregnancy include singleton, vertex presentation, term gestation and no precluding medical or obstetric risks. Planned birth center birth, N=15,574 Nulliparas, N=7355, 47.2% of sample	Perinatal mortality rate for women admitted in labor (excluding lethal anomalies) 0.87/1000 Other neonatal outcomes reported: Neonatal transfer Incidence and indication for emergency neonatal transfer		
Non-U.S.-based Studies				
Catling-Paull, 2013	Australia Retrospective cohort Non-comparative analysis of routinely collected data for 2005-2010 from the 12 publically-funded home birth	**Perinatal Mortality** (stillbirth and early neonatal death within 7d. for planned home birth group) 6/1807 (0.33%) Perinatal mortality excluding expected deaths of infants with lethal anomalies	**Cesarean Section** (for planned home birth group) Other outcomes reported: Place of birth Normal vaginal birth Assisted vaginal birth Vaginal breech birth	**Very Low (OOO+)** 9 of 12 programs participated in study, raising possibility of underreporting of poor outcomes. Australian health system, training, practice patterns, regulation of midwives and other

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Citation	Study Description	Fetal & Neonatal Outcomes#, +	Maternal Outcomes#	Study Quality* (GRADE) Comments
	programs in Australia at that time. Data was collected and stored by hospitals in which the home birth program was based. 3 smaller programs did not contribute data (55/1862 births). Publically funded home birth programs have strict low-risk criteria, including singleton gestation, 37-42 wks EGA, no medical, surgical, or obstetric/fetal risk factors. Despite these criteria, there were Nulliparas, N=575, 31.8% of study sample	1.7/1000 (0.17%) Other outcomes reported: 5 min Apgar score <7 BW Admission to special care nursery Neonatal morbidity (respiratory distress, hypoxic-ischemic encephalopathy) Breastfeeding initiation Breastfeeding at 6 weeks	Transfer to hospital before birth Transfer to hospital after birth Perineal trauma Episiotomy Management of 3rd stage	professionals are different from U.S. systems, and results may not be applicable to U.S. settings. Prior studies had raised questions about the safety of home birth in Australia and in 2001 the provision of home birth services by private midwives was in marked decline due to the collapse of international indemnity insurance. In a 2009 governmental national Maternity Services Review, the majority of public submissions related to homebirth, most of these from women who wanted access to the service. In response, the government established publically funded home birth in all states/territories with the exception of Queensland. The services operate within the public hospital system. Midwives are accredited, their cases subject to peer review and they engage in emergency training.
Davis, 2012	New Zealand Retrospective cohort Data from New Zealand College of Midwives research database for low-risk women giving birth in 2006 & 2007. Database included data for	No neonatal outcomes reported.	**Postpartum Hemorrhage** (PPH) (greater than 1000mL) Planned primary unit birth is referent category for each RR calculation (PPH in primary unit, 23/2904 [1.1%])	**Very Low (OOO+)** No analysis by parity. No report of neonatal outcomes. Limited to outcomes related to PPH. Did

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Citation	Study Description	Fetal & Neonatal Outcomes#, +	Maternal Outcomes#	Study Quality* (GRADE) Comments
	32% of all NZ births and is subject to regular audit and validation. Midwives in NZ are the primary caregivers for most women and care for women at home, in primary units (or birth centers), secondary- and tertiary-level hospitals. There is a nationally agreed set of consultation and referral criteria Low-risk births, N=16,453 (mean parity only reported as descriptive variable with home birth cohort having mean parity of 1.4)		Planned home birth 19/1830 (1.0%) crudeRR 0.93 (0.53-1.65) adjRR 0.93 (0.49-1.74) (adjusted for smoking, age, parity, ethnicity, augmentation, length of labor, mode of birth, episiotomy, perineal trauma, BW>4kg, and mode of third stage management) Planned secondary hospital 96/7359 (1.3%) crudeRR 1.2 (0.08-1.79) adjRR 1.07 (0.68-1.69) Planned tertiary hospital 67/4107 (1.6%) crudeRR 1.47 (0.96-2.24) adjRR 1.10 (0.67-1.79) No other relevant outcomes reported.	not report any critical outcomes. Indirectness present due to non-U.S. setting.
de Jonge, 2009	Netherlands Retrospective cohort National database of birth	Planned home v. Planned hospital birth **Intrapartum and neonatal death (0-7 days)**	No maternal outcomes reported.	**Very Low (OOO+)** Very large, 7 year, population-based national registry study.

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Citation	Study Description	Fetal & Neonatal Outcomes#, +	Maternal Outcomes#	Study Quality* (GRADE) Comments
	registrations Data for singleton, term (37-42 wks) births among low-risk women in primary midwifery care at onset of labor, planning either a home or hospital birth, using national registration database, for 7 years from 2000-2006. Planned home birth, N=312,307 Primiparous, 40.9% of study sample Planned hospital birth, N=163,261 Primiparous, 46.7% of study sample	[adjOR adjusted for parity, gestational age, maternal age, SES, ethnicity] adjRR 1.00 (0.78-1.27) Other outcomes reported: Intrapartum and neonatal death within 1d. NICU admission		Netherlands has national primary care midwifery, and home birth criteria, integrated system of home and hospital care with clear lines of responsibility for transfer and consultation. Study setting may not be applicable to U.S. settings.
Janssen, 2009	British Columbia, Canada Retrospective cohort Prospectively collected data of all planned home births attended by registered midwives (RM) compared to planned hospital births meeting eligibility requirements for home birth and attended by the same group of registered midwives	**Perinatal mortality rate** (intrapartum stillbirth or death in first 28 days of life) RM-Home: 0.35 (0.00-1.03)/1000 RM-Hosp: 0.57 (0.00-1.43)/1000 Phys-Hosp: 0.64 (0.00-1.56)/1000 Overall RR Perinatal Mortality (all parities)	**Cesarean delivery** CS-Nulliparous RM-Home: 158/1215 (13%) RM-Hosp: 453/2428 (18.7%) Phys-Hosp: 481/2204 (21.8%) CS-Multiparous RM-Home: 50/1684 (3.0%) RM-Hosp: 45/2324 (1.9%)	**Very Low (OOO+)** No analysis of perinatal mortality outcomes by parity. (Authors have been contacted to see if additional information available for outcomes by parity.) Perinatal mortality reported in text and tables as stillbirth and death within 7d., but group followed longer and no deaths occurred from days 7 through 28 in any

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Citation	Study Description	Fetal & Neonatal Outcomes#, +	Maternal Outcomes#	Study Quality* (GRADE) Comments
	from 2000 through 2004. A second comparison group of planned, home birth eligible, hospital births attended by physicians was included. RMs are required to offer women choice of planned delivery in home or hospital for those meeting College of Midwives of British Columbia eligibility requirements. These allow 1 prior CS, and require woman to be term (37-42 wks), singleton fetus, spontaneous labor or with outpatient induction method only, and absence of significant pre-existing or pregnancy-related disease. Provincial standards require RM to have baccalaureate degree in midwifery from a Canadian university. If trained outside of Canada they are required to pass written, oral and practice-based exams. Planned home—RM (RM-Home), n=2889 (41.9% nulliparous) Planned hospital—RM (RM-Hosp), n=4752 (51.1% nulliparous)	RM-Home v. RM-Hosp RR 0.61 (0.06-5.88) RM-Home v. Phys-Hosp RR 0.55 (0.06-5.25) Other outcomes reported: 1 and 5 min Apgar<7 Meconium aspiration Asphyxia at birth Birth trauma Resuscitation at birth BW<2500g Seizures Oxygen therapy >24h. Assisted ventilation>24h. Admission to hospital after birth or readmission if hospital birth	Phys-Hosp: 107/3127 (3.4%) Overall RR for CS (all parities and adj for parity) RM-Home v. RM-Hosp adjRR 0.76 (0.64-0.91) RM-Home v. Phys-Hosp adjRR 0.65 (0.56-0.76) Other outcomes reported: Electronic fetal monitoring Augmentation of labor Narcotic analgesia Epidural analgesia Assisted vaginal delivery Episiotomy 3rd or 4th degree perineal tear Postpartum hemorrhage Infection Pyrexia	group so we have reported this as the more conventional measure of PM. This study has the strength of controlling for birth attendant by use of the same group of midwives in both home and hospital settings. Quality rating is due to study being conducted outside of the U.S., but to the extent that there are similarities to situation in Oregon the results may be more applicable than for some other non-U.S. studies.

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Citation	Study Description	Fetal & Neonatal Outcomes#, +	Maternal Outcomes#	Study Quality* (GRADE) Comments
	Planned hospital—Physician (Phys-Hosp), n=5331 (41.3% nulliparous)			
Kennere, 2010	South Australia (SA) region of Australia Retrospective cohort Analysis of perinatal database of all births in SA, 2001-2006, plus additional information on perinatal deaths from expert committee reviews of all deaths in SA. Planned home birth, N=1141, 31.2%, nulliparas Planned hospital birth, N=297,192, 41.0% nulliparas All GA included, but proportions not specified.	**Perinatal Mortality, rate per 1000 births** (stillbirths and neonatal deaths up to 28d.): Planned home births 8.2/1000 Planned hospital births 7.9/1000 adjOR 1.38 (0.56-3.41) (Adjusted for maternal age, parity, occupational status, smoking, plurality, medical and obstetric complications, GA, SGA, congenital anomalies, type of hospital, mode of delivery.) Perinatal mortality standardized by GA 2.18 (0.87-4.50)/1000 Perinatal mortality standardized by BW groups 2.36 (0.95-4.86)/1000 Total perinatal deaths Home: 9/1141	**Cesarean birth:** Planned home birth 104/1136 (9.2%) Planned hospital birth 79,238/292,469 (27.1%) adjOR 0.27 (0.22-0.34) Other outcomes reported: Instrumental delivery Episiotomy 3rd or 4th degree perineal tear Postpartum hemorrhage	**Very Low (OOO+)** No information on types of home birth attendants or training and other systems of referral/transfer. Included all gestational ages >20 wks EGA and with BW >=400g, but little information about the population included in study, including proportions of women with risk factors such as breech, multiple gestation, or prior CS.

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Citation	Study Description	Fetal & Neonatal Outcomes#, +	Maternal Outcomes#	Study Quality* (GRADE) Comments
		Hospital: 2440/297,192 Attributed causes of 9 perinatal deaths--2 lethal congenital anomaly; 1 in context of waterbirth with limited monitoring at home; 1 second twin from intrapartum asphyxia; 1 hydropic fetus with non-lethal congenital anomaly; 1 growth restricted with suspected karyotype abnormality; 1 unexplained, but with tight nuchal cord x 4; 1 early gestation ROM resulting in pulmonary hypoplasia; 1 "seriously post-term" with refusal of all intervention. Other neonatal outcomes reported: Intrapartum deaths Deaths attributed to intrapartum asphixia 5 min Apgar <7 Specialized neonatal care		
Nove, 2012	UK, North West Thames Regional Health Authority Retrospective cohort 15 NHS hospitals in region, all using the computerized St. Mary's Infirmary Information System. Data from 1988-2000 for low	No neonatal outcomes reported.	(Only outcome reported) **Postpartum Hemorrhage (PPH) of >=1000ml** Risk of PPH, Hospital v. Home crudeOR 2.7 (no CI, p<0.001) adjOR 2.5 (1.7-3.8) Risk of PPH, Hospital v. Home	**Very Low (OOO+)** Database included "most" hospitals in region, but how many not included not specified. Sample may not be considered low risk by current standards (no upper limit on GA, no specification on what meant by high-risk pregnancy) which may have introduced selection bias. Data from time period as late as 1988 and up to 2000, in system different from U.S.,

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Citation	Study Description	Fetal & Neonatal Outcomes#, +	Maternal Outcomes#	Study Quality* (GRADE) Comments
	risk pregnancies planning a home or hospital birth, and that did not have medical induction of labor, elective cesarean, GA<37 wks, unplanned home birth, and which resulted in live births or stillbirths. Planned home birth, N=5998 Planned hospital birth, N=7874		Primiparas: crudeOR 1.7 (no CI, p<0.001) adjOR 2.0 (1.9-2.2) [model adjusted for pregnancy risk status, suspected macrosomia, prior BW <4500g, BMI, borderline anemia, parity, age, ethnicity, BW, infant sex, # ultrasound scans in pregnancy, yr of birth, hospital providing care, time of day of delivery]	thus contributing to indirectness. No critical outcome reported.
van der Kooy, 2011	Netherlands Retrospective cohort Data from the Netherlands Perinatal Registry for planned home and hospital births, attended by a community midwife, taking place from 2000-2007. Subjects met low-risk national criteria and were eligible for planned birth in either location. Note that this study overlaps with the series of studies by de Jonge. Planned home birth:	**Perinatal Mortality** (stillbirth and neonatal death within 7d.) Planned home birth 594/402,912 (0.15%) Planned hospital birth 403/219,105 (0.18%) Planned home v. planned hospital birth, risk of PM *crudeRR* 0.80 (0.71-0.91) *adjRR* 1.05 (0.91-1.21) (adjusted for intended place of birth, parity,	No maternal outcomes reported.	**Very Low (OOO+)** Outcomes not reported by parity. Perinatal mortality outcome includes neonatal deaths to 7d. rather than to 28d. The Netherlands has national primary care midwifery, and home birth criteria, integrated system of home and hospital care with clear lines of responsibility for transfer and consultation. Study setting may not be applicable to U.S. settings.

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Citation	Study Description	Fetal & Neonatal Outcomes#, +	Maternal Outcomes#	Study Quality* (GRADE) Comments
	Total (all parities) N=402,912 Primiparas, N=171,986 Multiparas, N=230,926 Planned hospital birth: Total (all parities) N=219,105 Primiparas, N=104,249 Multiparas, N=114,856	age, ethnicity, neighborhood, GA, SGA, prematurity, low Apgar score, congenital abnormality.) [note: RR for primiparas v. multiparas was presented in Table 2, but mixed intended place of birth such that abstractable data by parity not available.] Other outcomes reported: GA at birth Proportions in categories of SGA, prematurity, low Apgar score, and congenital abnormality, for each planned birth location.		

Evidence table presents outcomes of fetal/neonatal death under neonatal outcomes and data on incidence of Cesarean delivery under maternal outcomes when it was reported by the study. If those data not available then next most relevant outcome abstracted for table. Additional outcomes reported by study are listed in each column. Primary available outcome indicated in bold text. Specific and subgroup analyses are indicated by underlining outcome.

+ Measures of effect presented when possible with 96% Confidence Interval (CI) when available, the CI is indicated by placing it in parentheses after the measure of effect.

*Study quality based on most relevant/critical perinatal/neonatal mortality/morbidity outcome reported in study unless otherwise indicated

Table Abbreviations: adjOR-adjusted OR; adjPM-adjusted perinatal mortality; adjRR-adjusted relative risk; AMU-planned alongside midwifery unit birth; BW-birth weight; CI-confidence interval; CNM-certified nurse midwife; CO-composite outcome; CPM-certified professional midwife; crudeOR-basic OR without any adjustment; CS-cesareean section; d-days; DM-diabetes; EGA-estimated gestational age; FMU-planned freestanding midwifery unit birth; GA-gestational age; GDM-gestational diabetes; GRADE- Grading of Recommendations Assessment, Development and Evaluation HELLP-hemolysis, elevated liver enzymes, low platelets; Home-planned home birth; htn-hypertension; ICU-intensive care unit; OOH-Out of Hospital; OR-odds ratio; p-p-value; PPH-postpartum hemorrhage; PN-prenatal; PRBCs-packed red blood cells; N-number of subjects in study or group; NHS-National Health Service (UK); NICU-neonatal intensive care unit; OR-odds ratio; OU-planned obstetric unit birth; OVD-operative vaginal delivery; PM-perinatal mortality; RM-registered midwife; ROM-rupture of membranes; RR-relative risk; SGA-small for gestational age; SVD-spontaneous vaginal delivery;

Study Quality (OOO+) represents very low, (OO++) represents low.

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Table C3. GRADE Evidence Profile (Quality Assessment) for Primary Outcomes, New Search, by Study

Quality Assessment							
Design	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**	**Quality Rating**	**Outcome Importance**
5 min Apgar score <4 (Cheng, 2013; US, vital stats)							
observational studies	serious[1]	no serious inconsistency	serious[2, 3]	no serious imprecision	increased effect for RR ~1[2]	OOO+ VERY LOW	IMPORTANT
Perinatal Mortality (intrapartum stillbirth to 28d.) (Cheyney, 2014; US, MANA registry)							
observational studies[4]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	OO++ LOW	CRITICAL
Fetal/Neonatal Composite Outcome (Birthplace, 2011; UK)							
observational studies[5]	no serious risk of bias	no serious inconsistency	serious[6]	no serious imprecision	none	OOO+ VERY LOW	CRITICAL
Perinatal/Neonatal (intrapartum stillbirth to 28 d) Mortality (Hutton, 2009; Ontario, Canada)							
observational studies	no serious risk of bias	no serious inconsistency	serious[6]	no serious imprecision	none	OOO+ VERY LOW	CRITICAL
Perinatal Mortality (intrapartum stillbirth to 28d) (de Jonge, 2015; Netherlands)							
observational studies	no serious risk of bias	no serious inconsistency	serious[6]	no serious imprecision	none	OOO+ VERY LOW	CRITICAL
Severe Combined Maternal Morbidity (de Jonge, 2013; Netherlands)							
observational studies	no serious risk of bias	no serious inconsistency	serious[6]	no serious imprecision	none	OOO+ VERY LOW	IMPORTANT
Perinatal Mortality (intrapartum stillbirth and neonatal deaths) (Johnson, 2005; US, NARM CPM study)							
observational studies	serious[7]	no serious inconsistency	serious	no serious imprecision	none	OOO+ VERY LOW	CRITICAL
Perinatal Mortality (intrapartum stillbirth to 7d) (Stapleton, 2013; US, birth center)							
observational	no serious risk	no serious	no serious	no serious	none	OO++	CRITICAL

Quality Assessment							
studies[8]	of bias	inconsistency	indirectness	imprecision		LOW	
Perinatal Mortality (intrapartum stillbirth to 7d) (Catling-Paull, 2013; Australian publically-funded home birth programs)							
observational studies[9]	serious[10]	no serious inconsistency	serious[6]	no serious imprecision	none	OOO+ VERY LOW	CRITICAL
Postpartum Hemorrhage (>=1000mL) (Davis, 2012; New Zealand)							
observational studies	no serious risk of bias	no serious inconsistency	serious[6]	no serious imprecision	none	OOO+ VERY LOW	IMPORTANT
Perinatal Mortality (intrapartum stillbirth to 7d) (de Jonge, 2009; Netherlands)							
observational studies	no serious risk of bias	no serious inconsistency	serious[6]	no serious imprecision	none	OOO+ VERY LOW	CRITICAL
Perinatal Mortality (intrapartum stillbirth to 28d.) (Janssen, 2009; British Columbia, Canada)							
observational studies[11]	no serious risk of bias	no serious inconsistency	serious[6]	no serious imprecision	none	OOO+ VERY LOW	CRITICAL
Perinatal Mortality (stillbirth to 28 days) (Kennare, 2009; South Australia)							
observational studies	serious[12]	no serious inconsistency	serious[6]	no serious imprecision	none	OOO+ VERY LOW	CRITICAL
Postpartum Hemorrhage (>=1000mL) (Nove, 2012; North West Thames, England)							
observational studies	serious[13]	no serious inconsistency	serious[6]	no serious imprecision	none	OOO+ VERY LOW	IMPORTANT
Perinatal Mortality (intrapartum stillbirth to 7d) (van der Kooy, 2011; Netherlands)							
observational studies[14]	no serious risk of bias	no serious inconsistency	serious[6]	no serious imprecision	none	OOO+ VERY LOW	CRITICAL

Table Footnotes:

[1] Vital statistics--US birth certificates--substantial differences among OOH and hospital birth cohorts--although logistic regression to attempt control of residual confounding was undertaken may still be substantial unmeasured confounding. No info on validity of measure by each group of providers/site of birth.

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[2] If planned home birth mother or infant transferred to hospital then outcome attributed to hospital. This could have created bias against hospital and positively for home. However, the outcome numbers for home setting are small and all ORs are highly overlapping such that determination of plausible confounding effect for this surrogate outcome is uncertain.

[3] Surrogate outcome used

[4] Large, prospective data collection, non-comparative, registry study

[5] Large prospective study of planned home, planned midwifery units and planned obstetric unit births with high quality control and sophisticated analysis

[6] Non-US based study, closely regulated midwifery, with defined system of consultation and transfer.

[7] 4% of CPMs did not participate after registering in study. If these stopped study/CPM re-certification process because of poor outcomes could have introduced a negative bias on measures of effect.

[8] Large, prospective data collection, non-comparative study of planned birth center birth

[9] Small, non-comparative study

[10] 3 of 12 programs did not participate in study. Represented small numbers of births, but if poor outcome and participation linked then could introduce confounding.

[11] Provincial BC perinatal databases used to compare same midwives attending low-risk, home birth eligible women for planned home or hospital birth, and second comparison group of women receiving physician care in hospital.

[12] Included all births over 20 wks EGA and BW 400g, which could contribute bias to either group depending on care patterns and referral. There was robust inquiry into perinatal deaths.

[13] Data from time older time period, as late as 1988 and up to 2000. Database included "most" hospitals in region, but how many not included not specified. Sample may not be considered low risk by current standards (no upper limit on GA, no specification on what meant by high-risk pregnancy) which may have introduced selection bias.

[14] Data may overlap with de Jonge, 2009 and de Jonge, 2015

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APPENDIX D. APPLICABLE CODES

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
V22	Normal pregnancy
V23	Supervision of high-risk pregnancy
V24	Post-partum care and examination
ICD-10 Diagnosis Codes	
Z34	Encounter for supervision of normal first pregnancy, unspecified trimester
O09	Supervision of high-risk pregnancy
Z39	Encounter for care and examination of mother immediately after delivery
ICD-9 Volume 3 (Procedure Codes)	
72	Forceps, vacuum and breech delivery
73	Other procedures inducing or assisting delivery
74	Cesarean section and removal of the fetus
75	Other obstetric operations
CPT Codes	
59400-10	Vaginal delivery
59412	External cephalic version, with or without tocolysis
59414	Delivery of placenta (separate procedure)
59425-6	Antepartum care only
59430	Postpartum care only (separate procedure)
59510-15	Cesarean delivery
59610-22	Delivery after previous cesarean
HCPCS Level II Codes	
H1000-5	Prenatal care, at risk assessment

Note: Inclusion on this list does not guarantee coverage

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APPENDIX E. HERC GUIDANCE DEVELOPMENT FRAMEWORK

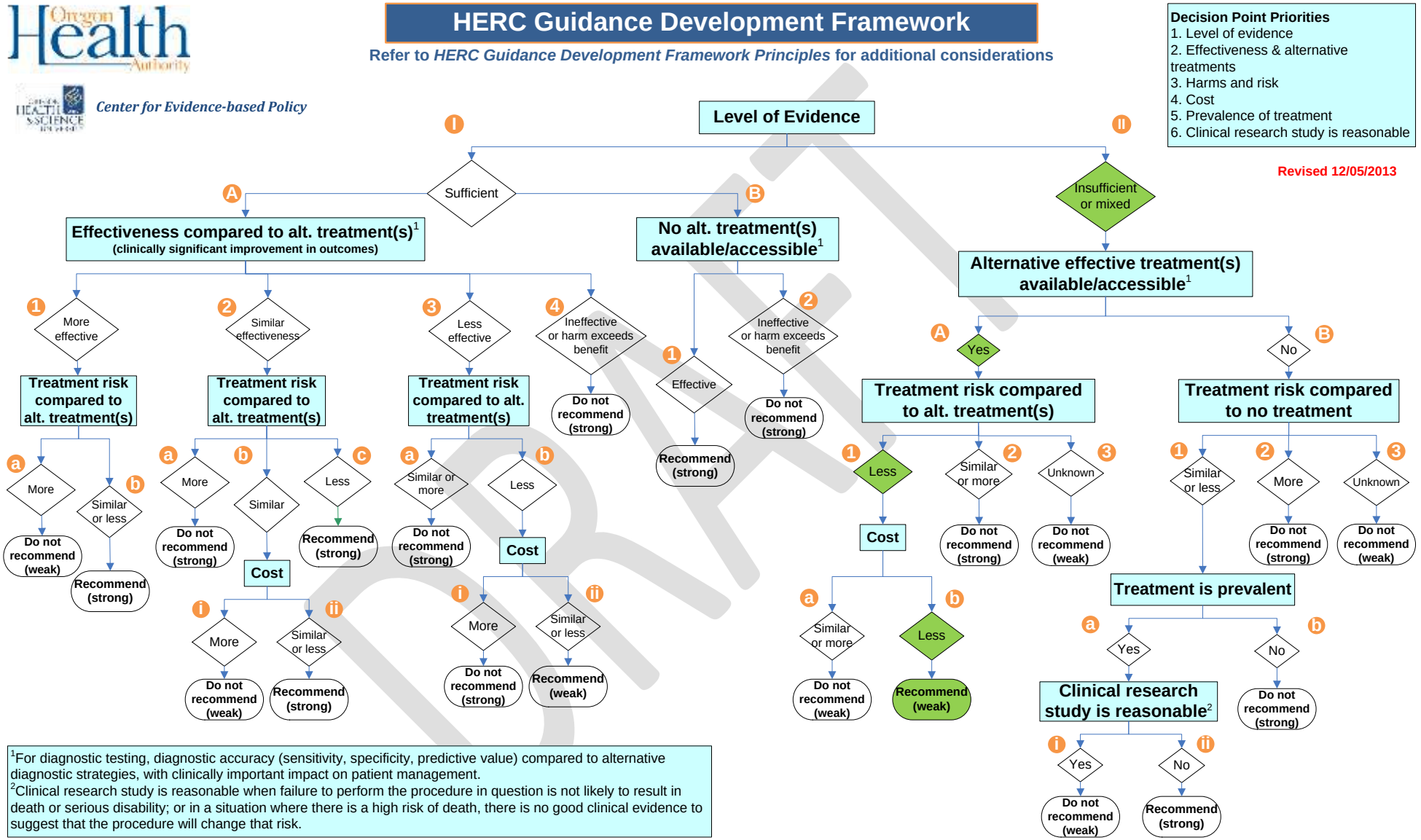
HERC Guidance Development Framework Principles

This framework was developed to assist with the decision making process for the Oregon policy-making body, the HERC and its subcommittees. It is a general guide, and must be used in the context of clinical judgment. It is not possible to include all possible scenarios and factors that may influence a policy decision in a graphic format. While this framework provides a general structure, factors that may influence decisions that are not captured on the framework include but are not limited to the following:

- Estimate of the level of risk associated with the treatment, or any alternatives;
- Which alternatives the treatment should most appropriately be compared to;
- Whether there is a discrete and clear diagnosis;
- The definition of clinical significance for a particular treatment, and the expected margin of benefit compared to alternatives;
- The relative balance of benefit compared to harm;
- The degree of benefit compared to cost; e.g., if the benefit is small and the cost is large, the committee may make a decision different than the algorithm suggests;
- Specific indications and contraindications that may determine appropriateness;
- Expected values and preferences of patients.

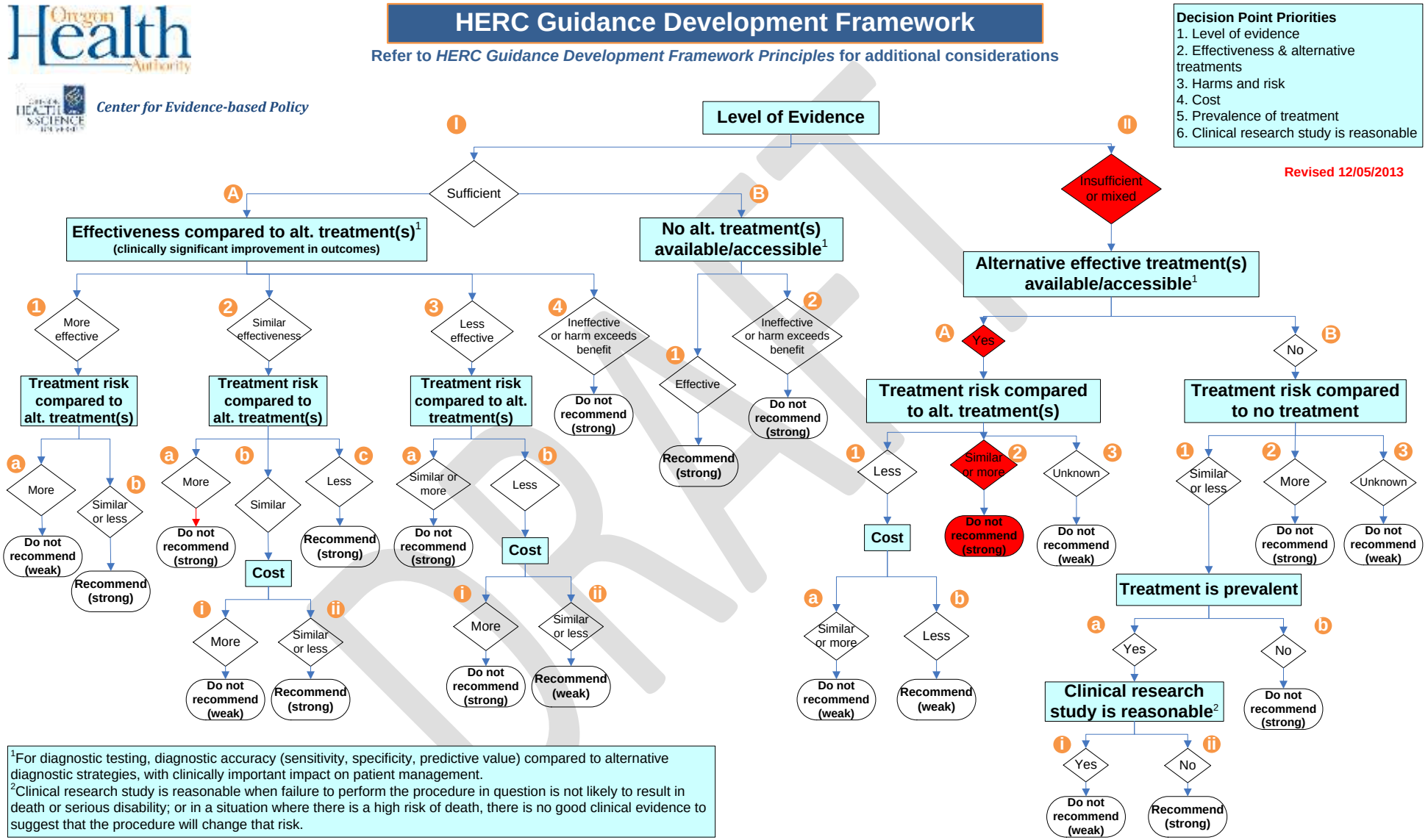
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Planned out-of-hospital birth for low-risk pregnancies



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Planned out-of-hospital birth for unselected pregnancies



[1]For diagnostic testing, diagnostic accuracy (sensitivity, specificity, predictive value) compared to alternative diagnostic strategies, with clinically important impact on patient management.
[2]Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

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Coverage Guidance: Planned out-of-hospital birth and Prioritized List

Question: How shall the Coverage Guidance on Planned Out-of-hospital birth be applied to the Prioritized List?

Question source: Licensed Direct Entry Midwifery workgroup; Evidence-based Guidelines Subcommittee

Issue: The EbGS has approved a draft Coverage Guidance for when coverage is recommended for out of hospital birth. VbBS needs to evaluate application to the Prioritized List of Health Services. Given the concerns about implementation, the subcommittee last time agreed that each of the risk factors would need to be addressed, with the exceptions of those for which further clinical or diagnostic assessment would only be necessary if suspicion for these arose (specific with asterisks* these conditions).

Proposed List changes:

1) **Adopt a new Guideline Note on Planned Out-of-hospital Birth.**

Guideline Note XXX PLANNED OUT-OF-HOSPITAL BIRTH

Lines 1,2

Planned out-of-hospital birth is included on these lines when appropriate risk assessments are performed, and the consultation and transfer criteria are followed, and no high risk coverage exclusion criteria exist. Risk assessment should be done initially when planning the location of birth, and updated throughout pregnancy, labor, and delivery to determine if out-of-hospital birth is still appropriate.

The clinical and/or diagnostic assessment of each criterion, with the exception of those marked with an asterisk, is necessary for planned out-of-hospital birth to be included on these lines. (Criteria marked with an asterisks may not be known or not be pertinent if there is no clinical indication for concern and additional diagnostic testing is not indicated.)

An ultrasound is required to rule out certain risk criteria (e.g. multiple gestation, placenta previa, and life threatening congenital anomalies). Certain risk criteria require serial measurements such as fundal height and blood pressure.

If a woman refuses a required clinical or diagnostic assessment, then ascertainment of her risk status is unknowable and she does not meet criteria for coverage for an out-of-hospital birth.

Documentation of continuing appropriate risk assessment and routine prenatal care is required.

High-risk coverage exclusion criteria:

Complications in a previous pregnancy:

Maternal surgical history

- Cesarean section or other hysterotomy
- Uterine rupture
- Retained placenta requiring surgical removal
- Fourth-degree laceration without satisfactory functional recovery

Maternal medical history

- Pre-eclampsia requiring preterm birth
- Eclampsia
- HELLP syndrome

Fetal and placental

- Unexplained stillbirth/neonatal death or previous death related to intrapartum difficulty
- Baby with neonatal encephalopathy
- Placental abruption with adverse outcome

Complications of current pregnancy:

Maternal

- Induction of labor
- Prelabor rupture of membranes > 24 hours
- Pre-existing chronic hypertension; Pregnancy-induced hypertension with diastolic blood pressure greater than or equal to 90 mmHg or systolic blood pressure greater than or equal to 140 mmHg on two consecutive readings taken at least 30 minutes apart
- Eclampsia or pre-eclampsia
- Anemia – hemoglobin less than 8.5 g/dL
- Thrombocytopenia (platelets <100,000)
- Thrombosis/thromboembolism/ or other maternal bleeding disorder*
- Maternal mental illness requiring inpatient care*
- Drug or alcohol use with high risk for adverse effects to fetal or maternal health
- Unknown, or positive, syphilis, HIV, or Hepatitis B status
- Current active infection of varicella at the time of labor; rubella infection anytime during pregnancy; active infection (outbreak) of genital herpes at the time of labor*

- Refractory hyperemesis gravidarum*
- Diabetes, type I or II, uncontrolled gestational diabetes, or gestational diabetes controlled with medication

Placental

- Low lying placenta within 2 cm or less of cervical os at term; placenta previa, vasa previa
- Placental abruption/abnormal bleeding
- Recurrent antepartum hemorrhage
- Uteroplacental insufficiency*

Fetal

- Gestational age - preterm or postdates (defined as gestational age < 37 weeks + 0 days or > 41 weeks + 6 days)
- Multiple gestation
- Non-cephalic fetal presentation
- IUGR (defined as fetal weight less than fifth percentile using ethnically-appropriate growth tables, or concerning reduced growth velocity on ultrasound)*
- Oligohydramnios or polyhydramnios*
- Abnormal fetal heart rate/Doppler/surveillance studies
- Blood group incompatibility with atypical antibodies, or Rh sensitization
- Molar pregnancy

Transfer criteria:

If out-of-hospital birth is planned, certain intrapartum and postpartum complications may necessitate transfer to a hospital to meet coverage criteria. For these indications, an attempt should be made to transfer the mother and/or her newborn; however, imminent fetal delivery may delay or preclude actual transfer prior to birth.

Maternal

- Temperature ≥ 38.0 C
- Maternal infection (endometritis, UTI, wound, breast)
- Hemorrhage (hypovolemia, shock, need for transfusion)
- Retained placenta > 60 minutes
- Laceration requiring hospital repair (e.g., extensive vaginal, cervical or third- or fourth-degree trauma)
- Enlarging hematoma
- Bladder or rectal dysfunction

Fetal and uterine

- Repetitive or persistent abnormal fetal heart rate pattern
- Thick meconium staining of amniotic fluid

- Prolapsed umbilical cord
- Failure to progress/failure of head to engage in active labor
- Chorioamnionitis or other serious infection (including toxoplasmosis, rubella, CMV, HIV, etc.)
- Uterine rupture, inversion or prolapse

If the infant is delivered out-of-hospital, the following complications require transfer to a hospital for the out-of-hospital birth to meet coverage criteria:

- Low Apgar score (< 5 at 5 minutes, < 7 at 10 minutes)
- Weight less than 5th percentile for gestational age
- Unexpected significant or life-threatening congenital anomalies
- Respiratory or cardiac irregularities, cyanosis, pallor
- Temperature instability, fever, suspected infection or dehydration
- Hyperglycemia/hypoglycemia unresponsive to treatment
- Hypotonia, tremors, seizures, hyperirritability
- Excessive bruising, enlarging cephalohematoma, significant birth trauma
- Vomiting/diarrhea

Consultation criteria:

Certain high risk conditions require consultation (by a provider of maternity care who is credentialed to admit and manage pregnancies in a hospital) for coverage of a planned out-of-hospital birth to be recommended. These complications include (but are not limited to) patients with:

Complications in a previous pregnancy:

Maternal

- More than three first trimester spontaneous abortions, or more than one second trimester spontaneous abortion
- More than one preterm birth, or preterm birth less than 34 weeks 0 days in most recent pregnancy
- Pre-eclampsia, not requiring preterm birth
- Cervical insufficiency/prior cerclage
- Third degree laceration; fourth-degree laceration with satisfactory functional recovery
- ~~Perinatal death~~
- Life-threatening congenital anomalies (unless fatal anomalies with nonresuscitation planned)
- Postpartum hemorrhage requiring additional pharmacologic treatment or blood transfusion
- Retained placenta requiring manual removal

Fetal

- Child with congenital and/or hereditary disorder
- Baby > 4.5 kg or 9 lbs 14 oz
- Shoulder dystocia, with or without fetal clavicular fracture
- Unexplained stillbirth/neonatal death or previous death unrelated to intrapartum difficulty
- Unresolved intrauterine growth restriction (IUGR) or small for gestational age (defined as fetal or birth weight less than fifth percentile using ethnically-appropriate growth tables)
- Blood group incompatibility, and/or Rh sensitization

Complications of current pregnancy:

Maternal

- Inadequate prenatal care (defined as less than five prenatal visits or care began in the third trimester)
- Body mass index at first prenatal visit of greater than 35 kg/m^2
- History of maternal seizure disorder (excluding eclampsia)
- Gestational diabetes, diet-controlled
- Maternal mental illness (with suspicion for psychosis or potential harm to self or infant) under outpatient psychiatric care
- Maternal anemia with hemoglobin < 10.5 g/dL
- Third-degree laceration not requiring hospital repair
- Laparotomy during pregnancy
- ~~High grade Cervical dysplasia requiring evaluation *~~

Fetal

- Fetal macrosomia (estimated weight >4.5 kg or 9 lbs 14 oz)
- Confirmed intrauterine death
- Family history of genetic/heritable disorders that would impact labor, delivery or newborn care

Table 1. High risk conditions proposed for additions/~~deletions~~/modifications disposition

The HERC received many public comments on the list of proposed "High risk conditions necessitating consultation or transfer." It was deemed more suitable that high risk conditions should be divided into separate lists; one encompassing conditions that would indicate planned hospital birth (or transfer), the other noting those conditions where consultation would be appropriate to assure the appropriateness of planned out of hospital birth.

In the table below, conditions that were raised as concerns in public comments are listed to the left. Disposition of these items to a list indicating consultation or transfer/planned hospital birth is noted, and sources cited.

	Pregnancy Complication (Comment)	Consultation required for coverage	Planned hospital delivery/transfer to hospital required for coverage	Source(s)	Recommendation/ Rationale
1	Gestational age of 36 weeks (proposed modification to minimum low-risk criteria)		X (preterm, GA <37w0d)	NICE guideline	Low-risk criteria were clarified. Intention is 36 **completed** weeks of pregnancy (i.e. 37 weeks + 0 days) as recommended by NICE is required to be considered low-risk; therefore any point during 36th week requires transfer.
2	Pregnancy past 41 weeks (proposed modification to minimum low-risk criteria)		X (postdates, GA >41w6d)	NICE guideline recommends 41 completed weeks. Oregon Birth Center risk criteria place the upper limit at 43 weeks, or 42 weeks with abnormal non-stress test.	Low-risk criteria were clarified. Intention is to be consistent with NICE guidance on **completed** weeks of pregnancy. Box language was modified to indicate upper limit is 41 weeks + 6 days.
3	Prior Cesarean section (proposed addition to minimum low-risk criteria)		X	NICE guideline, Table 6	EbGS agrees that patients with prior Cesarean section are not low-risk for out-of-hospital birth, it is considered an exclusion criteria for OOH birth coverage recommendation. See comment F15, commenter cites two studies.

	Pregnancy Complication (Comment)	Consultation required for coverage	Planned hospital delivery/transfer to hospital required for coverage	Source(s)	Recommendation/ Rationale
4	Ultrasound between 12-30 weeks (proposed addition to minimum low-risk criteria)			HERC Coverage Guidance on Ultrasound in Pregnancy	Not added to low-risk criteria based on previous evidence review finding no change in management of pregnancy based on routine ultrasound.
5	Diabetes, pre-existing or gestational (proposed addition)	X (Gestational, diet- and exercise-controlled only)	X (Type I, Type II, uncontrolled gestational, or gestational controlled with medication)	Oregon LDM low-risk criteria and birth center absolute risk criteria exclude existing diabetes, uncontrolled GDM or GDM controlled with medication. NICE guideline lists diabetes as an indication for hospital birth. Ontario suggests transfer of care for insulin-requiring diabetics and consultation for those unresponsive to dietary treatment. Netherlands guidance lists diabetes as indicating secondary-level obstetric care.	Previously was incorporated into nonspecific language about maternal disease. EbGS added gestational diet- and exercise -controlled diabetes mellitus to consultation and all other types as indications for planned hospital birth.
6	Having had an IUD (proposed addition)			Netherlands lists "Status following removal of the IUD" as category A (midwife/GP)	Not added to list based on absence of evidence of risk.

	Pregnancy Complication (Comment)	Consultation required for coverage	Planned hospital delivery/transfer to hospital required for coverage	Source(s)	Recommendation/ Rationale
7	Extremes of maternal age (proposed addition; prior box language said age <14)			NICE recommends consultation for maternal age >35 but does not put a lower age limit on home birth. Guidelines from British Columbia specify age less than 17 or over 40 as indication for discussion, and age less than 14 as indication for consultation.	Commenters suggest <17 should be an indication for hospital birth, sources only recommend consultation for age less than 14. EbGS decided to strike these recommended criteria for consultation based on lack of evidence that age in of itself is a criterion necessitating consultation in the absence of other factors.
8	Prior third-degree laceration (proposed addition in E2) Prior fourth-degree laceration (proposed deletion in F9)	X		NICE lists "Extensive vaginal, cervical, or third- or fourth-degree perineal trauma" as a consultation indication; Netherlands guidance recommends midwife/GP care if function was restored (category A) and secondary obstetrical care if it was not (category C).	EbGS decided to require consultation for third - or fourth degree lacerations, and to require planned hospital birth where function has not been restored after a prior fourth-degree laceration.

	Pregnancy Complication (Comment)	Consultation required for coverage	Planned hospital delivery/transfer to hospital required for coverage	Source(s)	Recommendation/ Rationale
9	Intrapartum third- or fourth- degree laceration (proposed deletion in F24)		X	British Columbia and Ontario list third and fourth degree lacerations as indicating consultation. Netherlands lists fourth-degree laceration as an indication for transfer to secondary obstetrical care.	Laceration requiring hospital repair (e.g., extensive vaginal, cervical or third/fourth degree trauma), is included in box language on the list of intrapartum complications requiring transfer. Coverage guidance could be further amended to include third- or fourth-degree laceration not requiring hospital repair as an indication for consultation without transfer 4th degree and 3rd degree requiring hospital repair requires transfer to hospital. 3rd degree not requiring hospital repair requires consultation.
10	Prior fractured clavicle and shoulder dystocia (proposed addition)	X		NICE guideline: NICE lists shoulder dystocia as an indication for planned hospital birth. Fetal clavicular fracture would presumably be secondary to dystocia so we have added clarification.	EbGS discussed that definition is challenging and ultimately determined that consultation should be obtained to elicit specific circumstances & severity, and determine likelihood of recurrence.
11	Maternal Jehovah's Witness status (proposed addition)			No evidence sources	No evidence was discovered or provided to support inclusion of maternal objection to transfusion as a high-risk condition. EbGS discussed that the reason for transfer would be to obtain blood products, which would be refused by the patient, so this was not added.

	Pregnancy Complication (Comment)	Consultation required for coverage	Planned hospital delivery/transfer to hospital required for coverage	Source(s)	Recommendation/ Rationale
12	Maternal seizure disorder/epilepsy (proposed addition)	X Maternal seizure disorder (excluding eclampsia)		Netherlands B if medicated NICE guideline indicates transfer regardless of medication status	Core sources differ. Medication use may not be a good proxy for risk level, and labor seldom triggers an underlying seizure disorder. EbGS discussed and ultimately decided to require consultation in this condition.
13	Prior infant > 9 lbs (proposed addition)	X (History of baby >4.5kg or 9lb14oz)		NICE guideline	NICE recommends history of previous baby >4.5kg as an indication for consultation.
14	Suspected macrosomia (proposed addition)	X (Suspected fetal macrosomia EFW >4.5kg or 9 lbs 14 oz)		NICE guideline	Suspicion of macrosomia in the current pregnancy is also an indication for consultation and was therefore also added.
15	Incomplete prenatal testing e.g. strep, STI, GDM (see comment G12) (proposed addition)	X (inadequate prenatal care (defined as less than 5 prenatal visits or care began in the third trimester)	X Unknown HIV or Hepatitis B status	USPSTF recommends the following screening tests & preventive services for pregnant women: EtOH misuse screening; bacteriuria screening; breastfeeding counseling; CT & GC; GDM screening; HIV; iron-deficient anemia screening; syphilis screening; tobacco use counseling NICE recommends screening if mother is willing on booking.	Women with inadequate prenatal care face increased risk regardless of birth setting, so this by itself should not exclude home birth as an option. EbGS decided that unknown HIV or HBV status should warrant a planned hospital birth, as early interventions could make a difference to the newborn.
16	Severe mental health issues not well-controlled (proposed addition)	X (Maternal mental illness under outpatient	X (Maternal mental illness requiring inpatient care)	NICE lists “psychiatric disorder requiring current inpatient care” as an indication for hospital birth, and “Under current outpatient	Follow more specific NICE guideline.

	Pregnancy Complication (Comment)	Consultation required for coverage	Planned hospital delivery/transfer to hospital required for coverage	Source(s)	Recommendation/ Rationale
		psychiatric care)		psychiatric care" as an indication for consultation. Under the Netherlands guidance, psychiatric illness is category B (consultation situation), noting severity and extent of the disorder will determine the best course.	
17	Intrapartum or postpartum complications (proposed deletion)				EbGS feels it is important to note intrapartum and postpartum complications of mother and infant that would necessitate transfer to a higher level of care. This does not imply that the services provided by an out of hospital provider who was compliant with the guidance prior to development of a complication, who then transferred the patient(s) appropriately, would not be covered.
18	History of preterm birth (proposed deletion)	X		NICE does not list a history of preterm birth as a high-risk indication. A history of preterm birth is listed by Netherlands guidance as category B (consultation situation). Ontario guidance recommends consultation for "History of more than one preterm birth, or preterm birth less than 34 weeks 0 days in most recent pregnancy."	Continue to include certain prior preterm births as requiring consultation to be consistent with Netherlands and Ontario guidance.

	Pregnancy Complication (Comment)	Consultation required for coverage	Planned hospital delivery/transfer to hospital required for coverage	Source(s)	Recommendation/ Rationale
19	History of more than three first trimester spontaneous abortions, or more than one second trimester spontaneous abortion (proposed deletion)	X		Ontario guidance	Retain box language including history of spontaneous abortions (i.e. miscarriage) as requiring consultation as taken from the Ontario guidance
20	Failure to progress/ failure of head to engage in active labor (proposed deletion)		X	Oregon birth center states this as a reason to transfer. Both the Ontario and Netherlands guidance recommend it as an indication for consultation.	EbGS discussed that consultation would result in a recommendation to transfer, so requiring transfer for failure to progress makes more sense.
21	Cervical dysplasia requiring evaluation (proposed deletion)	X		Netherlands guidance	Retain requirement as recommended by The Netherlands, which lists this as category B (consultation situation).
22	Hyperemesis gravidarum (proposed deletion)		X	Hyperemesis requires secondary level care until it is resolved (Netherlands guidance). Ontario and British Columbia also list refractory hyperemesis as an indication for consult.	Keep as a transfer criteria, but modify to "refractory hyperemesis gravidarum"
23	Family history of genetic/heritable disorders (proposed deletion)	X		Guidance from British Columbia lists "Family history of genetic disorders, hereditary disease or significant congenital anomalies" as an indication requiring consultation.	Retain to follow guidance from British Columbia, because some (but not all) heritable disorders require hospital care for the neonate in the immediate postpartum period.

	Pregnancy Complication (Comment)	Consultation required for coverage	Planned hospital delivery/transfer to hospital required for coverage	Source(s)	Recommendation/ Rationale
24	History of pre-eclampsia/HELLP syndrome (proposed deletion)	X (if did not necessitate preterm birth)	X (if necessitated preterm birth)	NICE lists history of pre-eclampsia as necessitating individual assessment; and history of pre-eclampsia requiring preterm birth as an indication for planned hospital birth. Netherlands lists prior HELLP syndrome as an indication for secondary care (category C).	Commenter requests further refinement if this is to be included (see comment F 10) Box language modified to align with NICE/Netherlands on when consultation vs transfer necessary for history of pre-eclampsia.
25	History of unexplained stillbirth/neonatal death or previous death related to intrapartum difficulty (proposed deletion)	X (unexplained stillbirth/neonatal death or previous death unrelated to intrapartum difficulty)	X (unexplained stillbirth/neonatal death or previous death related to intrapartum difficulty)	NICE guidance does include "Unexplained stillbirth/neonatal death or previous death related to intrapartum difficulty" as a condition indicating planned hospital birth. History of unexplained stillbirth is listed in multiple sources (Netherlands, Ontario, and British Columbia) as requiring consultation.	Commenter says this is a broad category best suited to careful evaluation, consultation and informed consent. Gives example of cord accident. (See comment F 11) Retain requirement of transfer to follow NICE guidance when related to intrapartum difficulty. Consult appropriate for unexplained stillbirth unrelated to intrapartum difficulty.
26	History of postpartum hemorrhage requiring additional treatment or blood transfusion (proposed deletion)	X	~~X~~	NICE guideline	This language is being retained as it is taken directly from NICE as an indication for planned hospital birth, however, it is unclear as to what "additional treatment" entails; e.g. is intramuscular oxytocin "additional treatment?" As there are a variety of possible scenarios, EbGS elected to make it a condition requiring consultation.

	Pregnancy Complication (Comment)	Consultation required for coverage	Planned hospital delivery/transfer to hospital required for coverage	Source(s)	Recommendation/ Rationale
27	History of retained placenta requiring manual removal (proposed deletion)	X (if manual removal was required)	X (if surgical intervention was required)	NICE guideline	Commenter says this will exclude women with histories that are not actually clinically concerning for the current pregnancy, and that ultrasound evaluation is the appropriate course of action. However, even with ultrasound evaluation, the patient is at increased risk of undetected abnormal placentation. EbGS accepted expert recommendation to require a hospital birth only if surgical removal was required, and consultation for a history of manual removal.
28	Placenta previa, vasa previa, low lying placenta (proposed modification)		X (Complete placenta previa or low lying placenta within 2 cm or less of the cervical os at term; known vasa previa)	Oregon birth center absolute risk criteria list "Low-lying placenta within 2 cm or less of cervical os; vasa previa; complete placenta previa" as prohibiting admission to the birth center. NICE table 7 lists "Placenta praevia" as a complication of current pregnancy indicating birth at an obstetric unit.	Commenter asked that this be clarified to specify placenta previa at term. Language modified to follow the combined criteria in Oregon Birth Center ARC and NICE guideline, and address commenter's concern.
29	Confirmed intrauterine death (proposed deletion)	X		NICE lists "Confirmed intrauterine death" as a complication of current pregnancy indicating birth at an obstetric unit. In addition, "Dead fetus" is Netherlands C (requiring secondary obstetric care); however, Ontario guidelines list "Intrauterine fetal demise" as an indication for	Commenter expressed that the only risk to the mother is if there are signs of infection or DIC after the passage of significant time, and suggested that families should have home birth as an option after consultation and informed consent if safe. Coverage guidance language is made to be

	Pregnancy Complication (Comment)	Consultation required for coverage	Planned hospital delivery/transfer to hospital required for coverage	Source(s)	Recommendation/ Rationale
				consultation only.	consistent with Ontario recommendation.
30	Body mass index at first prenatal visit of greater than 35 kg/m^2 (proposed deletion)	X		NICE criteria list "BMI at booking > 35 kg/m^2" as a complication of current pregnancy indicating birth at an obstetric unit.	Commenter expressed that many larger women are excellent candidates for home birth if other risk factors are absent and recommended allowing home birth after consultation. EbGS decided to make it a requirement for consultation as risks are higher for some women and not for others, such as those that have had a number of uncomplicated prior births
31	Small for gestational age fetus (proposed modification)	X Prior pregnancy with unresolved IUGR or small for gestational age (defined as fetal or birth weight less than fifth percentile using ethnically-appropriate growth tables)	X Intrauterine growth restriction (IUGR) (defined as fetal weight less than fifth percentile using ethnically-appropriate growth tables, or concerning reduced growth velocity on ultrasound)	NICE guideline	As noted by commenter, NICE specifies < 5th percentile or reduced growth velocity on ultrasound as indicating planned hospital birth. Coverage guidance was edited to clarify this, with additional language to specify ethnically-appropriate growth tables.
32	Fetal growth retardation (proposed modification)	X (also see SGA/IUGR above)	X (also see SGA/IUGR above)		Has been changed as requested to "Intrauterine growth restriction (IUGR)" for consistency. This is an indication for consultation in a prior pregnancy and planned hospital birth in current pregnancy, and is defined as <5%ile using

	Pregnancy Complication (Comment)	Consultation required for coverage	Planned hospital delivery/transfer to hospital required for coverage	Source(s)	Recommendation/ Rationale
					appropriate growth tables.
33	Prelabor rupture of membranes > 24 hours (proposed deletion)		X	NICE recommends transfer to obstetric care after "rupture of membranes more than 24 hours before the onset of established labour." Netherlands guidance also recommends secondary obstetric care after 24 hours (category C).	Language retained to follow NICE/Netherlands guidance that rupture of membranes >24 hours is indicated for hospital birth. Commenter F said that risk of infection is small after 24 hours especially in home birth setting with minimal vaginal exams and recommends it be included in informed consent. Commenter G suggested > 18 hours as increasing chance for sepsis and necessitating other treatment.
34	Genital herpes (proposed modification)		X (current active infection)	NICE guideline	Conflicting public comments (any history of genital herpes vs. active.) Guidance language changed to "Current active infection (outbreak) of genital herpes at the time of labor. " "Current active infection of varicella at the time of labor" in accordance with NICE and to address one commenter's concern. Rubella infection anytime during pregnancy.
35	Thick meconium staining of amniotic fluid (proposed deletion)		X Possibly add language about imminent birth. Leave out language	Under Oregon birth center ARC, transfer is required for "Thick meconium-stained amniotic fluid without reassuring Doppler heart tones and birth is not imminent."	Commenter said this should be considered individually and expressed concern about imminent deliveries. Revise language to include "Thick

	Pregnancy Complication (Comment)	Consultation required for coverage	Planned hospital delivery/transfer to hospital required for coverage	Source(s)	Recommendation/ Rationale
			about reassuring tones.	Thick meconium is Netherlands C (secondary obstetric care) and is an indication for planned hospital birth.	meconium staining of amniotic fluid." As an indication for transfer. Together with the indication about fetal heart rhythm, this matches the Oregon Birth Center ARC. Language about imminent deliveries was added, but not specifically to this indication.
36	Retained placenta (proposed deletion)		X	NICE recommends urgent transfer if uterine exploration is necessary. Ontario lists it as a consultation indication. Netherlands category C (secondary care)	Commenter says the provider will need to determine safest course based on clinical picture, and this is covered in rule and practice standards. Retained placenta is an indication for transfer to a hospital, whether or not management by an out-of-hospital provider is initiated before or during transfer.
37	Retained placenta >1 hour (proposed modification)		X (after 60 minutes)	Oregon birth center criteria list a 3-hour cutoff. NICE, Netherlands, Ontario, and British Columbia guidances do not define a time cutoff for retained placenta. NICE defines retained placenta as no delivery within 30 minutes of the birth with active management or within 60 minutes of the birth with physiological management.	Original box language recommended transfer for retained placenta without a defined time cutoff. A 60 minute cutoff has been added to coverage guidance to be consistent with birth center criteria.

	Pregnancy Complication (Comment)	Consultation required for coverage	Planned hospital delivery/transfer to hospital required for coverage	Source(s)	Recommendation/ Rationale
38	Written transfer plan needs to be in effect that the accepting OB and pediatrician agree with (proposed addition)				A "well-defined system of transfer" is in the document but no longer in the box language. EbGS made a recommendation to HERC to share with appropriate other bodies the concerns raised on this and other related issues that are not addressed in the box coverage language, per say.
39	History of a blood clot, or bleeding disorder (proposed addition)		X (blood clot, or other maternal bleeding disorder)	Bleeding or coagulation disorder is Netherlands Category C (secondary obstetric care) and bleeding disorder in the mother is a NICE criterion for planned hospital birth.	Alternate language added related to current maternal disorders to follow Netherlands/NICE criteria.
40	Maternal hemoglobin <11 (proposed modification)	X (Maternal hemoglobin <10.5)	X (Maternal hemoglobin <8.5)	NICE specifies 8.5-10.5 as indication for individual assessment.	Box language will be modified to reflect 10.5 as cutoff for consultation with 8.5 retained as cutoff for transfer.
41	History of a group B Strep septic infant (proposed addition)			NICE lists "Risk factors associated with group B streptococcus whereby antibiotics in labour would be recommended" as indicating birth in an obstetrical unit.	No change made as qualified providers in Oregon should administer group B strep prophylaxis outside the hospital setting and so this is not by itself a contraindication to out of hospital birth.
42	Pregnancy-induced hypertension, pre-existing hypertension (proposed modification)		X (Raised diastolic blood pressure over 90 mmHg or raised systolic blood pressure	NICE guideline indicates a raised diastolic blood pressure over 90 mmHg or raised systolic blood pressure over 140 mmHg on two consecutive readings taken 30 minutes apart as an indication for	Commenter requested that blood pressure > 140/90 before or after delivery be added as a risk factor. Box language was added to reflect NICE cutoffs for hypertension as an indication

	Pregnancy Complication (Comment)	Consultation required for coverage	Planned hospital delivery/transfer to hospital required for coverage	Source(s)	Recommendation/ Rationale
			over 140 mmHg on two consecutive readings taken 30 minutes apart)	planned hospital birth or transfer. Oregon birth center ARC specifies blood pressure >150/100 on at least two occasions.	for planned hospital birth.
43	Thrombopenia (proposed modification)		X (Thrombosis/thromboembolism/ thrombocytopenia (platelets <100,000), or other maternal bleeding disorder)	NICE guideline Oregon Birth Center Criteria	Commenter requested maternal platelet count < 150,000 as a high-risk indication. Another requested <100,000. The word "thrombopenia" has been changed to "thrombocytopenia" and a cutoff of 100,000 is being added for consistency with NICE.
44	Chorioamnionitis or other serious infection *with fever >38 C* (proposed modification)		X		No change. Box language presently includes "chorioamnionitis or other serious infection." Maternal temperature is only one piece of the diagnostic criteria for chorioamnionitis. Temperature ≥ 38.0 C is a separate transfer criteria.
45	Blood group incompatibility (proposed deletion)		X (with atypical antibodies ~~or Rh sensitization~~)	NICE lists "atypical antibodies which carry a risk of haemolytic disease of the newborn" as indicating birth in an obstetrical unit. Active blood group incompatibility is Netherlands category C (secondary obstetric care).	The coverage guidance has been revised to include "Blood group incompatibility *with atypical antibodies,* or Rh sensitization" as an indication for hospital birth to align with NICE.
46	Substance abuse, including marijuana (proposed addition)	~~X~~ (~~routine use of alcohol or marijuana~~)	X (substance ~~misuse~~abuse or	NICE Table 7 lists both "Substance misuse" and "alcohol dependency requiring assessment or treatment"	There was an extensive discussion about the appropriate language to use to delineate problematic substance use and

	Pregnancy Complication (Comment)	Consultation required for coverage	Planned hospital delivery/transfer to hospital required for coverage	Source(s)	Recommendation/ Rationale
			dependence)	as factors indicating planned hospital birth. Netherlands list "Use of hard drugs" as necessitating secondary obstetrical care. Ontario suggests consultation for "Significant use of drugs, alcohol, or other substances with known or suspected teratogenicity or risk of associated complications." British Columbia also recommends consultation for "Significant use of drugs, alcohol, or other toxic substances."	abuse. Decision made to require planned hospital birth in the case of "Drug or alcohol use with high risk for adverse effects to fetal or maternal health. "
47	Primiparity (proposed addition)			Birthplace & MANA studies (see memo). NICE recognizes increased risk of adverse neonatal events in primiparous women, but on balance recommends OOH birth should be offered using shared decision making with risk tables	No changes to guidance based on parity (see additional evidence search results in guidance document for details).

HERC Coverage Guidance – Out-of-hospital (OOH) Birth
Disposition of Public Comments

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Commenters

Identification	Stakeholder
A	OB-Gyn physician *[Submitted December 3, 2014]*
B	CPM, LDM *[Submitted November 18, 2014]*
C	CPM, LDM *[Submitted November 18, 2014]*
D	QHOC Medical Directors *[Submitted December 9, 2014]*
E	Health plan medical director *[Submitted Dec. 10, 2014]*
F	Oregon Midwifery Council *[Submitted Dec. 10, 2014]*
G	Health Plan Midwife Committee Chairman *[Submitted Dec. 10, 2014]*
H	Oregon Pediatric Society, Doernbecher Children's Hospital, OHSU, Portland, OR [*Submitted Dec. 12, 2014*]
I	LDM *[Submitted December 15, 2014]*
J	MD, Retired Ob/Gyn *[Submitted December 15, 2014]*
K	RN *[Submitted December 15, 2014]*
L	Epidemiologist and RN *[Submitted December 15, 2014]*
M	Community Health Plan *[Submitted December 15, 2014]*

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HERC Coverage Guidance – Out-of-hospital (OOH) Birth
Disposition of Public Comments

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A	1	Two items to consider: 36 weeks' gestation is technically preterm birth, not sure a great idea for preterm births to happen at home, so consider using >/= 37 weeks.	Box language has been clarified to emphasize greater than 36 and less than 41 completed weeks of pregnancy, which would encompass EGA 37 weeks 0 days through 41 weeks 6 days, consistent with NICE guidance. Preterm is also a transfer requirement in the coverage guidance so aligning these to be 37 weeks 0 days would be appropriate.	1
	2	I don't see either pre-gestational or gestational diabetes on your pregnancy complications list. Certainly both put moms and babies at higher risk than genital herpes.	Diabetes (uncontrolled gestational, gestational requiring medication, or pre-existing Type I or Type II) has been added to the list of high-risk coverage exclusion criteria for planned out-of-hospital birth; diet-controlled gestational diabetes has been added to the list of criteria for consultation prior to planned out-of-hospital birth.	5
B	1	I am a licensed midwife, practicing in Portland Oregon in a blended licensed midwife/nurse-midwife practice. We offer prenatal care, home birth and postpartum services to **low risk** women and strongly desire to include low income women in our client base. However, I am concerned that the proposed coverage guidelines for out of hospital birth is NOT based on quality research in terms of what constitutes low risk. I am requesting that your committee review the evidence on low risk (see below) and reissue your guidelines based on unbiased, research.	Commenter does not specify which criteria she disagrees with. EbGS does not believe their evidence sources are biased or poor quality.	NA
B	2	Making normal birth a reality: Consensus statement from the Maternity Care Working Party http://mothersnaturally.org/pdfs/UKNormalBirthDocument.pdf	This is a consensus statement on the definition of a normal birth. They define normal birth as the following: • women whose labor starts spontaneously, progresses spontaneously without drugs, and who give birth spontaneously; • women who experience any of the following provided they do not meet the exclusion criteria: ○ augmentation of labour	NA

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			○ artificial rupture of membranes (ARM) if not part of medical induction of labor ○ Entonox ○ Opioids ○ Electronic fetal monitoring ○ Managed third stage of labor ○ Antenatal, delivery or postnatal complications (including for example post partum hemorrhage, perineal tear, repair of perineal trauma, admission to SCBU or NICU Normal delivery excludes: • induction of labor (with prostaglandins, oxytocics or ARM) • epidural or spinal • general anaesthetic • forceps or ventouse • cesarean section • episiotomy While a list of references is provided, supporting evidence is not specifically discussed.	
B	3	http://www.bmj.com/content/330/7505/1416.full?ehom=	Duplicate of the above document.	NA
B	4	Citizens for Midwifery Resources Webpage http://cfmidwifery.org/resources/	Website states that Citizens for Midwifery are "a non-profit, volunteer, grassroots organization. Founded by several mothers in 1996, it is the only national consumer-based group promoting the Midwives Model of Care." No evidence specifically identified.	NA

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C	1	I heard that the HERC is currently taking public comment on what constitutes low-risk for out of hospital birth. I have read the draft recommendations and am concerned about the proposed recommendations because they appear to risk women out for a large number of things that midwives are trained and qualified to handle. This is important to me because I am both a home birth midwife and a mother who has (safe, successful) had out of hospital births. I am concerned because I've known women who have chosen to have unassisted births because of similar strict sets of risk criteria. There are many women, who, when denied coverage due to unreasonable risk factors, will refuse to go to a hospital and will then be exposed to greater risks because of a lack of provider at their birth.	EbGS bases its decisions on the balance of benefits and harms according to the best available evidence, while taking into account patient values and preferences and limited resources. We understand that women have strong and highly variable preferences and that this report is a coverage guidance, which defines when home birth should be reimbursed as a safe and effective service. The coverage recommendation language now distinguishes between complications requiring consultation and those which require transfer or planned hospital birth, recognizing that some conditions require a planned hospital birth or transfer of care, while other risk factors require consultation to evaluate an individual situation and inform the patient's decision and provider's recommendation about where to plan to have her baby.	NA
C	2	Oregon's licensed midwives and birth centers both have sets of reasonable risk criteria that could be used to define coverage for out of hospital birth. The Midwives Association of Washington State also has a well-researched set of risk criteria that could be used in this situation (http://www.washingtonmidwives.org/documents/MAWS-indications-4.24.08.pdf). Please consider using these pre-existing sets of criteria when you consider who to offer coverage to.	Oregon birth center risk criteria are included in the guidance document as Appendix A. No reference provided for Oregon licensed midwives risk criteria. Washington criteria are provided in Appendix 1 of this document. They are similar to the other risk criteria already included. Commenter does not identify which of the proposed criteria she disagrees with.	NA
D	1	The possibility of VBAC is concerning given that many hospitals, especially in rural areas, cannot even offer VBAC. It would not be acceptable for these hospitals to be back up. And it is concerning that a condition that is too high risk for a hospital would be acceptable to be done at home.	Box language already indicated that women with prior Cesarean are not considered low-risk (and thus not candidates for out-of-hospital birth). The coverage recommendation has been modified to clarify the requirement for risk assessment at intake, during prenatal care and during labor and specify high-risk coverage exclusion criteria, consultation criteria and transfer criteria.	3

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D	2	Teen pregnancy is also a higher risk condition	Guidelines from British Columbia specify age less than 17 or over 40 as indication for discussion, and age less than 14 as criterion for consultation. EbGS decided to strike these recommended criteria for consultation based on lack of evidence that age in and of itself is a criterion necessitating consultation in the absence of other factors.	7
E	1	Should any of the complications occur at any point in the pregnancy, there should be a re-evaluation to determine the risk/status level; a. Low risk criteria should include an ultrasound between 12 – 30 weeks (standard accepted practice); b. Low risk criteria should include maternal and paternal age parameters such as 18 – 45 years of age;	HERC's existing coverage guidance on Ultrasound in Pregnancy reports the following: "Routine US in early pregnancy (< 24 weeks) does not change patient management, substantially alter delivery modes, or improve health outcomes, at least not in high-resource settings." and "Evidence has not shown routine US in late pregnancy (> 24 weeks) to change patient management, affect delivery mode, or improve health outcomes." Not added to low-risk criteria based on previous evidence review finding no change in management of pregnancy based on routine ultrasound. Regarding age, see comment D2 and disposition. Our evidence sources make no mention of paternal age as a risk factor for planned home birth. Women with inadequate prenatal care face increased risk regardless of birth setting, so this by itself should not exclude out of hospital birth as an option. EbGS decided that unknown HIV or HBV status should warrant a planned hospital birth, as early interventions could make a difference to the newborn. Coverage recommendation has been updated to require risk assessment throughout prenatal and labor period.	4 7 15

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E	2	a. Complications should include having had an IUD in place; b. Complications should include third degree lacerations as well as fourth degree lacerations; c. Complications should include fractured clavicle and shoulder dystocia; d. Complications should include parental Jehovah's Witness status – due to inability to transfuse; e. Complications should include history of large babies (>9 pounds); f. Complications should include 'incomplete prenatal testing' such as strep and all STDs g. Complications should include VBACs (we agree with Cascade CCO); and h. Complications should include severe mental health issues not well controlled or addressed;	a. There is no evidence supporting history of IUD use as a high-risk condition in pregnancy. "Status following removal of the IUD" is Category A in the Netherlands guidelines. b. History of third or fourth--degree laceration in a prior delivery is listed as a criterion for consultation. History of fourth-degree laceration is listed as a criterion for consultation or planned hospital birth depending on whether functional recovery has been achieved (following Netherlands). For laceration requiring hospital repair, see comment F24. Intrapartum third- or fourth-degree laceration requires transfer, unless it is a third-degree laceration not requiring hospital repair, (which is an indication for consultation). c. Shoulder dystocia with or without fetal clavicular fracture in a previous pregnancy is a criterion for consultation. EbGS discussed that definition is challenging and ultimately determined that consultation should be obtained to elicit specific circumstances & severity, and determine likelihood of recurrence. d. No evidence is presented by commenter on Jehovah's Witness status. All women giving birth out of hospital should have a full informed consent procedure, including information about what would be done if transfusion is indicated but declined. Personal or cultural objection to transfusion is not found as risk exclusion criterion in other systems identified. e. NICE recommends consultation if a prior baby was > 4.5 kg; this appears in our recommendation. f. Inadequate prenatal care is listed as a criterion for consultation. However, because of the risk to the baby, unknown HIV or HBV status is a high-risk coverage exclusion criterion. g. Absence of prior cesarean or other hysterotomy is a minimum criterion for low-risk pregnancy	4 8, 9 10 11 13 15 3

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			h. Drug or alcohol use with high risk for adverse effects to fetal or maternal health requires hospital birth Maternal mental illness under outpatient psychiatric care has been added to coverage guidance as requiring consultation prior to planned out-of-hospital birth, consistent with NICE guidance in table 9. Maternal psychiatric illness requiring inpatient care is added as a high-risk coverage exclusion criterion, again consistent with NICE guidance (table 6).	46
E	3	I thought there was criteria regarding specific distance requirements from a hospital that could perform resuscitative procedures and emergency C-sections.	No such requirement was identified in any of the sources used to generate the risk criteria; EbGS declines to make coverage recommendation based on distance.	NA
F	1	I am writing on behalf of the Oregon Midwifery Council, which represents Direct-Entry Midwives in Oregon, to express my serious concern about the Draft Coverage Guidance on Planned Home Birth. Firstly, I am concerned that the HERC makes only a weak recommendation for the coverage of planned home birth for low risk pregnancies when the evidence is strong that planned home birth with a trained midwife in low risk pregnancies is a safe option for women and babies.	Thank you for your comment. "Weak recommendation" is a language that comes from the GRADE system and indicates the degree of confidence for a recommendation (see HERC methodology for details.) In this case, because of the potential for bias in the observational studies, the subcommittee elected to make a weak recommendation for coverage of planned out-of-hospital birth.	NA
F	2	Secondly, many items on the "High Risk Conditions" list are completely out of line with the research on the safety of planned home birth with midwives. The list is much longer than is appropriate for coverage guidance for a provider type that is both skilled at, and required by OAR to use, risk assessment, consultation, referral, and transfer of care as needed. The current draft "high risk" list would prevent many healthy pregnant women from accessing basic maternity care with the provider type and at the location of their choice.	The list of "high risk exclusion criteria" was compiled from the trusted sources utilized by the EbGS – the Netherlands, British Columbia, and Ontario guidances as well as the Oregon Birth Center absolute risk criteria. There are situations in which consultation is indicated to address appropriateness for home birth, but transfer to a hospital setting may not be required. The recommendation has been clarified to specify which conditions are high-risk coverage exclusion criteria, criteria for consultation, or criteria for transfer to hospital care. For some consultation criteria, coverage for out of hospital birth may still be	NA

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			recommended. See revised coverage recommendation language.	
F	3	The HERC itself identifies the Cochrane Review and the Guidelines on the Care of Healthy Women and Their Babies During Childbirth of the National Institute for Clinical Excellence as its only two trusted sources in its review of the evidence on planned home birth yet somehow arrives at a different conclusion than either of these sources. The Cochrane Review states clearly that there is no evidence to favor planned hospital or planned home birth for low risk women. In fact the review states, It seems increasingly clear that impatience and easy access to many medical procedures at hospital may lead to increased levels of intervention which in turn may lead to new interventions and finally to unnecessary complications. In a planned home birth assisted by an experienced midwife with collaborative medical back up in case transfer should be necessary these drawbacks are avoided while the benefit of access to medical intervention when needed is maintained. Increasingly better observational studies suggest that planned hospital birth is not any safer than planned home birth assisted by an experienced midwife with collaborative medical back up, but may lead to more interventions and more complications. (Olsen, Clausen 2012).	This information is correct, quoted from the Plain Language Summary in the Cochrane review (p. 2). The NICE guideline review does review other studies beyond the Cochrane review in making its recommendation as well. This coverage guidance does not favor either planned hospital birth or planned out-of-hospital birth for low risk women. Rather, the coverage guidance recommends that out-of-hospital birth be covered under health plans as a safe and effective option for low risk women, and defines indications which may put a woman and her baby at risk for poor outcomes in a planned or actual out-of-hospital birth based on a review of high-risk criteria from other internationally-recognized bodies.	NA
F	4	Additionally, the NICE guidelines explicitly state that, for low-risk women, out-of-hospital birth is "particularly suitable for them because the rate of interventions is lower and the outcome for the baby is no different compared with an obstetric unit (National Institute for Clinical Excellence 2014)." The HERC is charged with making an evidence based recommendation and it must remedy this significant departure from that obligation.	This information is correct. See comment F3 above.	NA

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F	5	While the HERC has identified a number of fully recognized, research based-risks for home birth such as multiple gestation, non-vertex presentation, and pre-existing disease in the mother that negatively impacts pregnancy outcomes (e.g. chronic hypertension), it has also included potential risk factors that are either not based in research or are absolutely not appropriate for inclusion in coverage guidance. Coverage guidance should be based on risks that can be identified at the start of care or upon reassessment at term. It is inappropriate to include emergency occurrences that the midwife could not have foreseen. If these occur, is this guidance asserting that the midwife should not be compensated for all care before and after the event?	This coverage guidance recommends coverage for out-of-hospital birth for women with low risk pregnancies. See comment F2.	NA
F	6	In addition, there are far too many risk factors included in this guidance that are outside of accepted guidelines in the US, Canada, and the UK (health systems with which we normally compare ourselves). The HERC Coverage Guidance on Planned Home Birth should only include those risk factors in the "High Risk" list that are based in high-quality evidence and are in common usage in comparable health systems that have good outcomes from out-of-hospital midwifery care such as Canada and the UK.	The risk factors included in this coverage guidance are all derived directly from the guidelines listed by the commenter. That said, systems of midwifery care in Canada and the UK are sufficiently distinct from those in the US as to make direct translation impractical. Not all conditions that are amenable to out-of-hospital management in those systems are appropriate for such in the US. See comment F2.	NA
F	7	Further, when the HERC creates such a lengthy list of "high risk" conditions (beyond those included in a basic absolute risk guideline) that would exclude a patient from coverage for home birth it circumvents the rights of low-income patients to make informed choices about their own health care. This draft "high risk" list is not equivalent to recommending against payment for an experimental or medically unnecessary surgery, it is actually a recommendation against coverage for basic maternity and newborn care for many healthy women experiencing normal pregnancies. Consider, for example, that a woman with a history of genital herpes with no outbreak in the past two years, who has hyperemesis until 14 weeks, but is able to gain weight normally, and has a brother with down syndrome is "risked" out three times even though she is a perfectly reasonable candidate for home birth as long as she does not have a herpes outbreak at the time of birth.	See comment F2.	NA

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F	8	There are a number of items that should be removed from the draft "High-Risk" list as they are not research-based and are not included in the high-risk or exclusion criteria from the 2014 Guidelines on the Care of Healthy Women and Their Babies During Childbirth of the National Institute for Clinical Excellence, The Indications for Discussion, Consultation, and Transfer of Care from the College of Midwives of British Columbia, or the Consultation and Transfer of Care Guidelines of the College of Midwives of Ontario, the three main Guidelines that the HERC has reviewed. Many of these items are absolutely appropriate for evaluation and consultation, but to exclude them from coverage is nonsensical because without the evaluation or consultation process we can't know if significant risk is found in that particular case.	See comment F2.	NA
F	9	The following items should be removed from the "High Risk" list for the above-stated reasons: Pregnancy past 41 weeks (The NICE guidelines specifically include pregnancy to 41+6 weeks) History of preterm birth History of fourth degree laceration History of more than three first trimester spontaneous abortions, or more than one second trimester spontaneous abortion Failure to progress/ failure of head to engage in active labor Cervical dysplasia requiring evaluation Hyperemesis gravidarum Family history of genetic/ heritable disorders Age < 14	See comment F2 as well as comments about specific criteria below. The risk factor for post-term pregnancy has been clarified to define low risk as than 41 **completed** weeks (that is, the cutoff is > 41 weeks, 6 days.) Our recommendation includes history of preterm birth as an criterion for consultation, following the Netherlands guidance, which rates it as category B (consultation) History of 4th-deg laceration is listed by Netherlands guidance as category A or C, depending on whether satisfactory function is restored. After discussion, EbGS recommends consultation when there is a history of third- or fourth-degree laceration in prior pregnancy. The recommendation has been clarified that without functional recovery requires hospital birth, with functional recovery requires consultation. Box language on history of abortions is taken from the Ontario guidance (consultation recommended) Failure to progress/engage is taken from the Oregon birth center	2 18 9 19 20

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			ARC. Both the Ontario and Netherlands guidance recommend it as a criterion for consultation. EbGS decided this should be a criterion for transfer, since that would be the purpose of consult. Cervical dysplasia requiring evaluation is Netherlands category B (consultation) Hyperemesis gravidarum is recommended by Netherlands guidance as requiring a higher level of care until resolved. Language was changed to say "refractory" hyperemesis gravidarum indicates planned hospital birth. Family history of genetic/heritable disorders is taken from the British Columbia guidance as requiring consultation Age < 14: Please see comment D2.	21 22 23 7
F	10	Beyond these, there are a number of items that should either be removed from the high-risk list for a variety of reasons or edited for clarity. I have addressed these items individually below: **History of Pre-eclampsia/ HELLP syndrome**. Of the three guidelines used in the HERC review, only the NICE guidelines do include history of pre-eclampsia but only if preterm birth was required. We know that risk of pre-eclampsia decreases for multiparas and we know that pre-eclampsia is a very broad diagnosis. While a history of pre-eclampsia may be a significant risk factor it should be further defined or specified if it is going to be included in the high risk list. For instance "HELLP syndrome and/or pre-eclampsia requiring preterm birth." All patients will be evaluated for signs of pre-eclampsia in each pregnancy which is the more appropriate risk assessment tool in this case.	NICE lists history of pre-eclampsia as necessitating individual assessment (table 8). Pre-eclampsia requiring preterm birth and history of HELLP syndrome in prior pregnancy are high-risk coverage exclusion criteria. Pre-eclampsia not requiring preterm birth is a criterion for consultation prior to planned out of hospital birth. See revised box language.	24
F	11	**History of Unexplained stillbirth/neonatal death or previous death related to intrapartum difficulty**. This is a broad category that is best suited to careful evaluation, consultation, and informed consent rather than use as a risk for coverage exclusion. There are many cases included in this category that could be	History of unexplained stillbirth is listed in multiple sources (NICE, Netherlands, Ontario, and British Columbia) as requiring consultation.	25

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		completely appropriate for a home birth, for instance a history of an intrapartum demise due to a cord accident should not exclude someone from a subsequent home birth. Additionally a person who had a previous unexplained stillbirth with no other past or current clinical risk factors could be an excellent candidate for home birth with full informed consent about the risks involved and should not face an additional financial hardship as a result of this choice.	NICE guidance does include "Unexplained stillbirth/neonatal death or previous death related to intrapartum difficulty" as a condition indicating planned hospital birth. Both of these are reflected in the updated box language. If unexplained stillbirth/neonatal death or previous death was related to intrapartum difficulty, planned hospital birth is indicated. Otherwise, consultation is indicated.	
F	12	**History of postpartum hemorrhage requiring additional treatment or blood transfusion.** The research is not clear as to whether history of postpartum hemorrhage is predictive of future postpartum hemorrhage (Prata 2011). If this item is to be included in the high risk list it should be further clarified so that it relates to truly concerning hemorrhages. A woman who had a 500 cc blood loss and received Pitocin for it ("further treatment") would currently be defined as high risk which is not appropriate. Perhaps it could be worded "Postpartum hemorrhage requiring blood transfusion."	NICE table 6 lists "primary postpartum hemorrhage requiring additional treatment or blood transfusion" as an indication for birth at an obstetric unit, and specifies "additional pharmacologic treatment or blood transfusion." As there are a variety of possible scenarios, EbGS decided to make this a condition requiring consultation. The Prata 2011 study cited was a prospective cohort conducted in Egypt with 2510 women experiencing singleton pregnancies. There were 93 cases of primary PPH in the cohort. The authors found that "history of PPH in a previous pregnancy increased the risk of PPH by almost 69 times" (OR 68.61, $p<0.001$), although this was based on only seven women with a history of PPH, five of whom had repeat PPH and two of whom did not.	26
F	13	**History of retained placenta requiring manual removal.** This item is concerning because it may exclude many women with histories that are not actually clinically concerning for the current pregnancy. History of retained placenta may or may not be predictive for future complications and the appropriate clinical course of action is ultrasound evaluation for abnormal implantation.	NICE table 6 lists "retained placenta requiring manual removal in theatre" as an indication for birth at an obstetric unit. EbGS accepted expert recommendation to require transfer only if surgical removal was necessary, and consultation for history of manual removal.	27
F	14	**History of shoulder dystocia**. While a history of shoulder dystocia is a risk factor for future births this is an item that should necessitate careful evaluation of the records and current pregnancy course and consultation to determine whether the risk is significant for the current pregnancy rather than immediate denial of coverage	See comment E2.	10

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		without evaluation. A woman with tightly controlled blood glucose levels in a subsequent pregnancy with a smaller baby is likely, for example, not to experience a repeat complication.		
F	15	**History of cesarean section**. The two studies that include significant numbers of out-of-hospital vaginal births after cesareans (where the increased risk of rupture from tocolytics is not a factor as they are outside of scope of practice) showed good outcomes for mothers and babies as long as no other significant risk factors (e.g. breech, twins) were present (Cheyney et al 2014, Stapleton et al 2013).	Our recommendation follows NICE table 6, which lists "Caesarean section" as a previous complication indicating birth at an obstetric unit. Stapleton et al 2013 is a retrospective cohort study of 15,574 women receiving care in US birth centers from 2007-2010. There were only 56 TOLACs in this cohort (0.004%), of which 39 (70%) had successful VBAC. Because of the very small sample size, the authors do not separately analyze outcomes by prior cesarean status. Cheney 2014 is a retrospective cohort study of 16,924 women who planned home births in the US between 2004-2010. This cohort included 1054 women with prior cesarean (0.06%), of whom 915 (87%) had successful VBAC. Authors found that TOLAC patients experienced "an increased risk of intrapartum fetal death, when compared to multiparous women with no prior cesarean (2.85/1000 TOLAC vs 0.66/1000 multiparas without a history of cesarean, P = 0.05)" and no increase in neonatal death.	3
F	16	**Placenta previa, vasa previa, low lying placenta**. This item should specify placenta previa at term as placenta previa in early pregnancy is not relevant and simply requires reevaluation. Low lying placenta should be removed as it is vague, not research-based and is not included in other relevant guidelines	NICE table 7 lists "Placenta praevia" as a complication of current pregnancy indicating birth at an obstetric unit. Oregon birth center absolute risk criteria list "Low-lying placenta within 2 cm or less of cervical os; vasa previa; complete placenta previa" as prohibiting admission to the birth center. Ontario guidelines list vasa previa and asymptomatic placenta previa persistent into third trimester as indications for antenatal consultation, and symptomatic previa as an indication for transfer.	28

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			Coverage guidance has been edited to specify "Low lying placenta within 2 cm or less of cervical os at term; placenta previa, vasa previa" as ahigh risk exclusion criterion.	
F	17	**Confirmed intrauterine death**. This is an odd item to include in the high risk list as it is not a risk for the mother unless there are signs of infection or DIC after the passage of significant time. A family who has had a confirmed intrauterine death should have the option to have a home birth covered if they have received informed consent and it is what they want for their care during such a personal and trying process. This is yet another item that should necessitate careful evaluation, consultation, and informed consent but is not a reason for exclusion from coverage.	NICE table 7 lists "Confirmed intrauterine death" as a complication of current pregnancy indicating birth at an obstetric unit. "Dead fetus" is Netherlands C (requiring secondary obstetric care); however, Ontario guidelines list "Intrauterine fetal demise" as an indication for consultation only. Coverage guidance is consistent with the Ontario recommendation, requiring consultation to determine risk.	29
F	18	**Body mass index at first prenatal visit of greater than 35 kg/m2**. BMI on its own is not appropriate for inclusion in the high risk list. Many larger women are excellent candidates for home birth as long as other risk factors, such as uncontrolled gestational diabetes or limited mobility are not present. This is another item for careful evaluation, consultation, and informed consent, not for exclusion from coverage	NICE table 7 lists "BMI at booking > 35 kg/m^2" as a complication of current pregnancy indicating birth at an obstetric unit; EbGS decided to make it a requirement for consultation as risks are higher for some women and not for others, such as those who have had a number of uncomplicated prior births.	30
F	19	**Small for gestational age fetus**. This item needs to be clarified so that it does not unnecessarily exclude babies who are small but well within normal limits. The NICE guidelines do include this risk factor but specify that they mean less than 5th percentile. Additionally, if this item is to be included in the high risk list it should be specified that ethnically specific charts should be used so that babies of smaller ethnicities are not erroneously identified.	As noted by commenter, NICE specifies < 5%ile or reduced growth velocity on US as indicating planned hospital birth. Coverage guidance was edited to clarify this, with additional language to specify ethnically-appropriate growth tables.	31 32
F	20	**Prelabor rupture of membranes > 24 hours.** While the risk of infection does seem to increase somewhat after 24 hours of ruptured membranes that risk is still small, especially in the home birth setting and with minimal vaginal exams and other interventions. This should be a matter for the informed consent of the client within the OARs and practice standards of the provider.	Our recommendation follows the Netherlands and NICE sources. Netherlands guidance recommends secondary obstetric care after 24 hours (category C). NICE recommends transfer to obstetric care after "rupture of membranes more than 24 hours before the onset of established	33

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			labour."	
F	21	**Genital herpes.** While this is an important risk factor and is already included in the OARs, it is not appropriate for all genital herpes to fall under the high risk list. Both the British Columbia and the Ontario College of Midwives guidelines call for transfer when there is an active herpes outbreak in labor or at rupture of membranes. Many HSV positive women are excellent candidates for homebirth as long as they do not have an outbreak at the time of labor.	Guidance language changed to "active infection (outbreak) of genital herpes" in accordance with NICE and to address one commenter's concern.	34
F	22	**Thick meconium staining of amniotic fluid.** While this is a recognized risk factor, this item is more appropriate for rule and practice standard and does not make sense in coverage guidance. Home birth providers will be in situations where they are dealing with thick meconium staining and each case will need to be considered individually by the provider taking into account distance from hospital, if delivery is imminent, and other factors.	Our inclusion of thick meconium as a factor requiring transfer is based rating as a Netherlands C (secondary obstetric care) indication. From the Netherlands guidance: "When one of the items mentioned below occurs, an attempt should still be made to achieve an optimal condition for further intrapartum care, whilst referral to secondary care may be urgent, depending on the situation. When referring from the home situation, the risk of transporting the woman also needs to be included in the considerations." Revise language to include "Thick meconium staining of amniotic fluid" as a criterion for transfer. Language about imminent deliveries was added, but not specifically to this criterion.	35
F	23	**Retained placenta**. This is a strange item to include in coverage guidance because retained placentas do happen and the provider at hand will need to determine what is the safest course of action depending on the clinical picture. There will be cases where the safest course of action will be administration of anti-hemorrhagics and/or attempted manual removal before or during initiation of transport to hospital. This	Retained placenta is an indication for transfer to a hospital, whether or not management by an out-of-hospital provider is initiated before or during transfer. Original box language recommended transfer for retained placenta without a defined time cutoff. A 60 minute cutoff has been added to coverage	36 37

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		is an item that should be, and is, in rule and practice standards but does not make sense for coverage guidance.	guidance to be consistent with birth center criteria. NICE recommends urgent transfer if uterine exploration is necessary. Ontario – consultation indication Netherlands – C (secondary care)	
F	24	**Third or fourth degree, or periuretheral, laceration.** This item is confusing for a coverage recommendation especially alongside "laceration requiring hospital repair" as third and fourth degree repairs are outside of our scope of practice, but sometimes a physician or nurse-midwife will come do these repairs in the home setting so as not to interrupt the postpartum period. For these reasons this item seems inappropriate for coverage guidance.	"Laceration requiring hospital repair (e.g., extensive vaginal, cervical or third- or fourth-degree trauma)" is listed in the box language as an intrapartum criterion for transfer to hospital. Third-degree laceration not requiring hospital repair is a criterion for consultation. Third-degree and fourth-degree laceration occurring in a previous pregnancy are listed as high-risk criteria necessitating consultation prior to planned out-of-hospital birth. This is consistent with NICE guidance as found in Table 9: "Extensive vaginal, cervical, or third- or fourth-degree perineal trauma." History of a fourth-degree laceration without satisfactory functional recovery is a criterion for planned hospital birth.	9 8
F	25	Please seriously reconsider the length and scope of the high-risk list. Healthy pregnant women who are covered by the Oregon Health Plan have a right to informed choice of provider type and place of birth. The HERC should be cautious in recommending against coverage for basic maternity and newborn care in healthy women and restrict its recommendations to those conditions that are truly high risk for an out of hospital setting.	Coverage guidance has been edited to reflect a distinction between high-risk coverage exclusion criteria, and criteria for consultation or transfer when planning out-of-hospital birth.	NA
G	1	As chairman of the Midwife Committee for the All Care Health Plan in Grants Pass, Oregon, I am writing to convey our concerns regarding the coverage guidance for planned home birth.	Thank you for your comments.	NA

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G	2	In addition to the concerns detailed below, we ask that a temporary rule change be made to not allow home births until the guidelines can be finalized. In their current state, we feel the guidance violates all aspects of the triple aim. If a bad maternal or fetal outcome occurs during a home birth that could have been prevented by improved guidelines, that decreases the quality of the patient's experience, directly lowers the quality of care, and will substantially increase the cost of care. Therefore, we ask that you seriously consider the additions/changes to the guidelines below.	Home birth is currently covered by fee-for-service Oregon Health Plan. HERC will review the Coverage Guidance and consider it in making potential changes to the Prioritized List of Health Services for the Oregon Health Plan. Once any changes to the Prioritized List are complete, rule changes would need to be made.	NA
G	3	Before getting to those specific details, there are other vital points we ask that you also consider. • Need for midwives to have appropriate malpractice insurance. • Need for increased litigation protection for OB and Pediatric physicians who take care of failed planned home births and/or their subsequent complications. • Patients who refuse to adhere the guidelines needs to sign an informed refusal consent form.	All women giving birth out of hospital should have a full informed consent procedure. System characteristics associated with safe out of hospital birth include a system of consultation and referral/transfer that can assure seamless care. Written agreements that cover consultation/referral/transfer and a well-defined and practiced system of transfer are important as noted in the coverage guidance document.	38
G	4	Below are our overall recommendations: • Gestational age should be between 37 weeks/0 days and 40 weeks/6 days, thereby preventing a preterm or postdates birth.	See comment A1.	1, 2
G	5	• Maternal age should be between 18 and 37 years old	See comment D2.	7
G	6	• Place of planned home birth should be less than 15 min from the hospital providing obstetrical and pediatric care. Our past experience has proven that transfer plans are poor at best, and significantly contribute to the maternal/fetal morbidity and mortality.	See comment E3.	NA
G	7	• Written transfer plan needs to be in effect that the accepting OB and pediatrician agree with.	A "well-defined system of transfer" is in the document but no longer in the box language as a characteristic of a successful home birth.	38

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HERC Coverage Guidance – Out-of-hospital (OOH) Birth
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ID	#	Comment	Disposition	High-Risk Table Line
G	8	• Increase the current time from 30 to 60 days where an infant stays on open card before being assigned to an appropriate health plan	Enrollment issues are outside the scope of this coverage guidance.	NA
G	9	• A first trimester screening should be done with an OB to establish the due date and review maternal history to decide if home birth is a viable option.	Other types of maternity care providers, including midwives as well as family physicians, are qualified to assess dating, maternal history, and infectious disease screening.	NA
G	10	• A 2nd trimester anatomy ultrasound done with an OB to rule out any gross physical abnormalities.	See comment E1.	4
G	11	• Subsequent revaluation by OB if any complication arises later in pregnancy.	Complications of pregnancy necessitating consultation or transfer are listed in the box language.	NA
G	12	• The following labs needs to obtained, as they constitute standard of care: CBC, type and screen, hepatitis B, HIV, syphilis, gonorrhea, chlamydia, urine toxicology screen, gestational diabetes screen and repeat CBC at 28 weeks gestational age, and group B Strep screen at 35+ weeks gestational age.	See comment E2 (f). Urine toxicology screening may be appropriate in some patients at higher risk but is not universally recommended. Some of these labs may not be obtained due to a variety of factors including patient preference. Inadequate prenatal care may be a proxy for measurement, and women may refuse one or more of these tests. NICE says: At the booking appointment, for women who choose to have screening, the following tests should be arranged: • blood tests (for checking blood group and rhesus D status and screening for haemoglobinopathies, anaemia, red-cell alloantibodies, hepatitis B virus, HIV, rubella susceptibility and syphilis), ideally before 10 weeks • urine tests (to check for proteinuria and screen for asymptomatic bacteriuria) • ultrasound scan to determine gestational age using: ○ crown–rump measurement between	15

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ID	#	Comment	Disposition	High-Risk Table Line
			10 weeks 0 days and 13 weeks 6 days ○ head circumference if crown–rump length is above 84 millimetres • Down's syndrome screening using: ○ 'combined test' at 11 weeks 0 days to 13 weeks 6 days • serum screening test (triple or quadruple) at 15 weeks 0 days to 20 weeks 0 days Then discusses 28 weeks, Etc. EbGS decided that unknown HIV or HBV status should warrant a planned hospital birth, as early interventions could make a difference to the newborn.	
G	13	Below are our other recommendation that would negate a home birth or require transfer to a hospital: • Complications in previous pregnancy/maternal medical history o History of 3rct or 4th degree laceration o History of prior fetal clavicle fracture o History of a blood clot, or bleeding disorder o History of a group B Step septic infant o History of gestational diabetes o History of diabetes mellitus (Type 1or Type 2) o History of prior birth weight 2'.. 9 lbs o Any history of genital herpes	Lacerations—see comments F9, F24. Fetal clavicle fracture—see comment E2 Bleeding or coagulation disorder is Netherlands Category C (secondary obstetric care) and bleeding disorder in the mother is a NICE criterion for planned hospital birth. NICE table 6 lists "Risk factors associated with group B streptococcus whereby antibiotics in labour would be recommended" as indicating birth in an obstetrical unit. However, qualified providers in Oregon may administer group B strep prophylaxis outside the hospital setting and so this is not by itself a high-risk coverage exclusion criterion for out-of-hospital birth. Diabetes mellitus and gestational diabetes mellitus—see comment A2. Genital herpes-see comment F21.	8, 9 10 39 41 5 34

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HERC Coverage Guidance – Out-of-hospital (OOH) Birth
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ID	#	Comment	Disposition	High-Risk Table Line
G	14	Complications in current pregnancy o Any patient who would refuse a blood transfusion, as any postpartum hemorrhage can turn into a life-threatening event o Prolonged rupture of membranes greater than 18 hours, thereby increasing chance of neonatal sepsis and necessitating other treatment o Maternal seizure disorder o Severe maternal psychiatric disease o Any undiagnosed vaginal bleeding o Maternal hemoglobin < 11 o Maternal platelet count < 150,000 o Suspected macrosomia o Substance abuse, including marijuana	See comment E2 regarding refusal of transfusion Prelabor rupture of membranes > 24 hours is a high-risk coverage exclusion criterion for planned out-of-hospital birth; none of the trusted sources provide evidence for an 18-hour cutoff. See also F20. Maternal seizure disorder: Netherlands B if medicated; should indicate consultation prior to planned home birth. Severe maternal psychiatric disease—see E2h. NICE specifies hemoglobin 8.5-10.5 as indication for individual assessment. Our recommendation specifies 10.5 as a consultation criterion and 8.5 as a high-risk coverage exclusion criterion. Abnormal bleeding is listed as an high-risk coverage exclusion criterion and a transfer criterion, based on Oregon Birth Center Criteria Thrombocytopenia is listed as a high-risk exclusion criterion, based on Oregon Birth Center and NICE criteria. Ontario lists it as an indication for consultation. See also comment J4. Fetal macrosomia is added as an criterion for consultation prior to planned home birth Drug or alcohol use with high risk for adverse effects to fetal or maternal health and mental health disorder requiring inpatient care are listed in box language as high-risk coverage exclusion criteria. Maternal mental illness under outpatient psychiatric care is a criterion for consultation.	11 33 12 16 40 39 43 14 16 46
G	15	• Transfer to hospital o Any meconium, not just thick meconium	Thick meconium is currently mentioned in the Oregon Birth Center absolute risk criteria.	35

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ID	#	Comment	Disposition	High-Risk Table Line
			Meconium (any) is Netherlands C (secondary obstetric care) British Columbia lists "thick or particulate meconium" as indication for consultation See revised box language and comment F22.	
G	16	We fully realize the volatile and emotional aspects of home birth. We admit that we have dealt with past disastrous maternal/fetal outcomes, and as such we feel very strongly about this issue. Again, in their current state, we feel the guidelines violate all three aspects of the triple aim. We ask for your consideration for the above details. If we can provide any more information, please feel free to contact us.	Thank you for your comments.	NA
H	1	The Oregon Pediatric Society provides the following public comment regarding Oregon's Home Birth Policy. When home births occur we support the American Academy of Pediatrics Policy Statement on Planned Home Birth: "The safest setting for a child's birth is a hospital or birthing center, but the AAP recognizes that women and their families may desire a home birth for a variety of reasons. Pediatricians should advise parents who are planning a home birth that AAP and ACOG recommend only midwives who are certified by the American Midwifery Certification Board. There should be at least one person present at the delivery whose primary responsibility is the care of the newborn infant and who has the appropriate training, skills and equipment to perform a full resuscitation of the infant. All medical equipment, and the telephone, should be tested before the delivery, and the weather should be monitored. A previous arrangement needs to be made with a medical facility to ensure a safe and timely transport in the event of an emergency. AAP guidelines include warming, a detailed physical exam, monitoring of temperature, heart and respiratory rates, eye prophylaxis,	Thank you for your comments and for including the American Academy of Pediatrics policy statement.	NA

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		vitamin K administration, hepatitis B immunization, feeding assessment, hyperbilirubinemia screening and other newborn screening tests. If warranted, infants may also require monitoring for group B streptococcal disease and glucose screening. Comprehensive documentation and follow-up with the child's primary health care provider is essential." Although not detailed above, "other newborn screening tests" would include newborn blood spot screening as described by the Northwest Regional Newborn Screening Program, pulse oximetry screening for critical congenital heart disease and newborn hearing screening.		
H	2	In practice, the manner by which infants are assessed for their candidacy for planned home birth is sometimes of concern. We agree that only those infants who are deemed "low risk" be candidates for home birth, but that their candidacy be determined based on widely accepted and complete prenatal care. This includes, but is not limited to a high quality prenatal ultrasound and completed testing for all routine maternal screenings, including HIV.	See comment E1.	15
H	3	Lastly, we believe the gestational age definitions included in the online report are too permissive. The March of Dimes has initiated successfully the "Healthy Babies are Worth the Wait" campaign to protect against elective birth prior to 39 weeks. This is because a broad literature describes the risks to infants born between 37 and 39 weeks which include respiratory difficulties, hypoglycemia, hypothermia, jaundice, feeding difficulties, learning challenges, and even death. We do not support planned home birth for infants < 37 weeks.	See comment A1. The literature referenced here applies primarily to non-spontaneous labor occurring prior to 37 weeks' gestation. Coverage recommendation on gestational age has been modified to 37 weeks 0 days through 41 weeks 6 days.	1, 2
I	1	This is to register my great concern on the HERC's guidelines on planned homebirth in Oregon. I have read the proposed guidelines and do not think these are in the best interest of childbearing women in Oregon. Although it is vital to understand and to educate that certain very high-risk	Thank you for your comments.	NA

ID	#	Comment	Disposition	High-Risk Table Line
		pregnancies will be better served in the hospital, using these (proposed) guidelines, in many cases, would rule out basic choice in basic maternity and newborn care for *HEALTHY WOMEN WHO ARE EXPERIENCING NORMAL PREGNANCIES.* Licensed midwives in Oregon work under risk assessment guidelines which are evidence-based and we continually assess and reassess women to evaluate who may need a consult with an MD or OB or other specialist and who may be too high risk for out of hospital birth.		
I	2	I have read [commenter F]'s letter to HERC on behalf of the Oregon Midwifery Council, and must say that I agree with [their] very specific comments, point by point, and I would refer you to that letter rather than renaming those points here. [Their} statements are a reflection of [their] extensive experience as a midwife and as an ardent researcher in the maternity care literature. As per [commenter F]'s letter, I agree that apparently, the HERC has identified certain risks for home birth that are truly research-based but has included as well many potential risk factors that are NOT based in research or that have no reason to be included in guidance for coverage. These items need to be addressed and hopefully removed from the list so that the HERC guidelines can be considered to have integrity and to be actually true to the task of providing "Evidence Based Recommendations." From my own limited experience as a midwife (>400 births) I can say that I have helped women with each of ([commenter F]'s named) risk factors and have had good outcomes. Risk assessment is an ongoing task for the midwife throughout the prenatal and birth and postnatal period, so that each woman and baby are assured the best outcomes.	See comments C1, C2, and F2.	NA
J	1	The ingredients necessary for good outcomes in out of hospital (OOH) births are not a secret. The literature shows that you need well-trained midwives, good transfer policies, and appropriate candidate selection. I agree with your concept of adopting coverage guidelines for Oregon that	Thank you for your comments.	38

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ID	#	Comment	Disposition	High-Risk Table Line
		incorporate the risk criteria used in Canada, UK, and the Netherlands.		
J	2	I have a few suggestions for changes in the wording that I think would improve the draft. "Planned Home Birth" should be changed back to "Planned Out-of-hospital birth." The coverage guidelines should pertain to all OOH births, both home and birth center. In Oregon, many birth attendants work both in birth centers and also do home births. Birth centers do not provide any additional safety features over home birth for high risk situations. The current birth center rules exclude twins and breech, but allow Previous C-section, postterm pregnancies up to 43 weeks, and hypertension up to 150/100. I think it is already confusing to the consumer that there are two sets of rules – one for LDMs through the BDEM, and another for Birth Centers. I think it would compound the confusion to have two sets of coverage guidelines.	The Licensed Direct Entry Midwife Staff Advisory Workgroup specifically requested the HERC to develop a coverage guidance related to planned home birth. The primary source (NICE) groups home birth and freestanding or alongside midwifery-led units as appropriate choices for low-risk women. In light of this, we have changed the title to "Planned out-of-hospital birth." It is appropriate to have a single set of criteria pertaining to all types of out of hospital births.	NA
J	3	In my view, "High risk conditions necessitating consultation or transfer include….." should be changed to "High risk conditions necessitating transfer to a hospital provider include……..." In Canada, the UK, and the Netherlands, the licensed midwives have admitting privileges to hospitals. The criteria for consultation and transfer apply to women who labor both in and out of hospitals. There are some patients who have high risk conditions that make them inappropriate candidates for OOH births, but whose labors can still be attended by midwives in the hospital in consultation with a physician. In Oregon, the vast majority of midwives who attend OOH births do not have hospital privileges, so high risk clients should be transferred to a provider with hospital privileges. Currently, Oregon rules for LDMs regarding consultations for high risk	Coverage guidance has been edited to reflect a distinction between exclusion criteria for coverage of planned out-of-hospital birth, and those that necessitate antepartum consultation with a provider who has expertise in caring for higher risk pregnancies and when planning out of hospital birth and the ability to admit to a hospital. See also comment F2 and revised coverage recommendations.	NA

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		clients, OAR 332-025-0021 (7) and (8), do not require that the consultation be with a physician with hospital privileges. The consultation can be with a physician, a PA, a CNM, a Naturopath, or another LDM with "direct experience". I believe the word "consultation" in your draft should be removed.		
J	4	I would recommend more precise definitions of certain risk criteria to avoid confusion. There are some discrepancies between the LDM rules, the birth center rules, and standard definitions in the medical literature. My suggestions are: a. "Fetal growth retardation" should be changed to "Intrauterine growth restriction". b. "Eclampsia, pre-eclampsia or pregnancy-induced hypertension, hypertension (before or after delivery) with blood pressure >140/90." Both ACOG and SOGC use a systolic of 140 or a diastolic of 90 to define gestational hypertension. (1,2) NICE (p. 30) recommends transfer to obstetric care for "either raised diastolic blood pressure (over 90 mmHg) or raised systolic blood pressure (over 140 mm Hg) on 2 consecutive readings taken 30 minutes apart." c. "Chorioamnionitis or other serious infection with fever >38 C." Three out of the eight OOH fetal/ neonatal deaths in Oregon in 2012 had chorioamnionitis. d. "Thrombopenia" should be changed to "Thrombocytopenia with platelets <100,000." e. "Uteroplacental Insufficiency and Intrauterine Growth Restriction." f. "Retained placenta >1 hour."	a. "Fetal growth retardation" language was taken from the Netherlands guidance and has been changed to "Intrauterine growth restriction" for consistency. b. Box language has been edited to reflect NICE cutoffs for hypertension as a criterion for transfer. c. Box language presently includes "chorioamnionitis or other serious infection" and temperature ≥ 38.0 C as separate transfer criteria. Maternal temperature is only one piece of the diagnostic criteria for chorioamnionitis. d. The word "thrombopenia" has been changed to "thrombocytopenia" for consistency. NICE table 6 does include cutoff of 100,000. e. "Uteroplacental insufficiency" and "Intrauterine growth restriction" are presently listed separately in the box language. f. Box language recommends transfer for retained placenta without a defined time cutoff. Oregon birth center criteria list a 3-hour cutoff. Netherlands, Ontario, and British Columbia guidances do not define a time cutoff for retained placenta. A sixty-minute cutoff has been added to coverage guidance to be consistent with NICE.	31 42 44 43 32 37
J	5	I think "failure to progress" also needs to be defined. Two out of the eight OOH fetal/neonatal deaths in Oregon in 2012 had prolonged labor. Some options: a. The Dutch criteria for failure to progress in the first stage of active	The definitions in a. through d. are correct. The box language does not presently include a definition of delay of labor. Defining "delay of labor" is a practice guideline definition outside the scope of	20

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		labor is "no change in the cervix or progress in dilation after the latent phase for a duration of 4 hours". Failure to progress in the second stage of labor is "lack of progress after a maximum of one hour, in cases with full dilation, ruptured membranes, strong contractions and sufficient maternal effort." b. NICE (p. 57) states that delay in the first stage of active labor is suspected if cervical dilatation is less than 2 cm in 4 hours. Diagnosis of delay in the active second stage (p. 60) is after 2 hours for nulliparous woman and one hour for multiparous woman. c. ACOG recently defined arrest of labor in the first stage of labor as no cervical change in 4 hours of adequate contractions or 6 hours of inadequate contractions. In the second stage, 2 hours of pushing in multiparous women and 3 hours in nulliparous women.(3) d. LDM rule OAR 332-025-0021 (5)(b)(F)(i) defines lack of adequate progress in second stage for vertex presentation "is when there is no progress after a maximum of three hours in cases with full dilation, ruptured membranes, strong contractions and sufficient maternal effort. (Note: In this rule, this situation is considered non-absolute and requires a consultation, but not necessarily transfer.) e. My preference is a hybrid: First stage – no change in the cervix or progress in dilation after the latent phase for a duration of 4 hours. Second stage – 2 hours of pushing in multiparous women and 3 hours in nulliparous women. (Non-emergency transport can take up to an additional hour.)	coverage guidance.	
J	6	For Postpartum complications, "Transfer to a higher level of care is recommended in the following circumstances:" should be changed to "The following post-partum complications require transfer to a hospital:"	Thank you for the suggestion. See revised box language.	NA
J	7	I agree that Previous Cesarean Section is a situation that should remain on the high risk list. In the recent MANAstats dataset of home births in the US, the intrapartum + neonatal death rate for term VBACs was 4.75/1000 compared to 1.24/1000 for	Thank you for your comment.	NA

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		women with no previous C-section in the same study. (4) OOH births use intermittent auscultation for fetal surveillance which is appropriate for low risk labors if done properly, but is not appropriate for VBACs. Quoting from the SOGC guidelines for intrapartum fetal surveillance: "For women attempting VBAC, there is little controversy. All professional jurisdictions recommend continuous electronic fetal monitoring." That includes ACOG, SOGC, and RCOG. (5)		
K	1	My name is [commenter K] and I am a licensed Registered Nurse in the state of Oregon. I have had the choice and privilege to birth my three children safely and gently at home over the past several years. I am pleased that you have put forth a great effort to lay out guidelines for women in Oregon who want more comprehensive choices in their prenatal care and birth experiences. I am also thankful that these choices will be more readily available to women on OHP and related health insurances. I am concerned, however, with some of the restrictions placed in the proposed guidelines, and fear that some of them may inappropriately hinder otherwise healthy candidates for home births with safe outcomes. Some of the proposed restrictions on what is defined as "high risk" pregnancy fail to take into consideration individual situations and the possibility of individualized care rather than providing "blanket labels" on what is or isn't "safe enough."	Thank you for your comments.	NA
K	2	My firstborn was born at 41 weeks and 2 days; 2 days beyond your recommended 36-41 week window, and I had a safe birth and healthy and safe outcomes for my child and myself. I understand that it is not uncommon for first births to be as much as 10 days late, give or take, with no adverse outcomes. I took care to monitor en-utero activity on a daily basis, as recommended both by my midwives, and also by literature I had received from an OB clinic before my transfer of care to a midwife team.	Thank you for sharing your experience. Cutoff of 41 weeks is endorsed by ACOG. NICE does include pregnancy up to 41 completed weeks, or 41 weeks+ 6 days. The coverage guidance language uses 41 completed weeks of gestation which comports with the NICE definition.	2
K	3	According to a simple calculator, I have a BMI over 35, but you would never guess that just looking at me. Just a few years ago, I was 5ft 6in and 180lb. (BMI about 30), but I was fit enough to run a 10K in one hour, thin enough to count all my ribs in the	NICE table 7 lists "Body mass index at booking of greater than 35 kg/m^2"as indicating increased risk, suggesting planned hospital	30

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		mirror, and lean enough to not be able to float in a pool to save my life. (I'd sink like a rock without actively swimming...it was impossible for me to do a dead-mans-float.) I had a flat stomach, and I ran a couple miles every day...but the BMI chart said I was overweight. Now, a little heavier and a little less active, I'm actually at just over a BMI of 35, but I'm still active, still healthy, have low cholesterol, and no indicators of diabetes, pre-diabetes, or high blood pressure. The typical BMI scale and chart doesn't accurately reflect my health status, but through an objective lens, a well-trained care provider would tell you that I'm a little overweight, but otherwise healthy. I know I'm not the only person like this. There are other women out there who are predisposed to higher muscle mass, whether genetically and/or through training. A BMI chart should be a tool in the overall evaluation of a candidate, not a defining point in whether or not services can or cannot be provided.	birth. EbGS decided to make it a criterion for consultation as risks are higher for some women and not for others, such as those that have had a number of uncomplicated prior births.	
K	4	I also have O- (RH negative) blood, and my husband has the Rh factor (Rh+), and all my children were consequently born with Rh+ blood, but I have had safe and healthy outcomes in all my pregnancies and births. My trained midwives were attentive to my needs and I had regular lab draws to monitor for any adverse reactions. A trained midwife is still a trained healthcare provider, and should be treated as such. Everything I was told that I would have available to me in the OB setting, I still had available to me in the midwife/home-birth setting of my care (Rhogam shots, appropriate and recommended lab draws, regular urine screening, blood glucose screening, newborn hearing screening, newborn lab draws, etc.)	Active blood group incompatibility is Netherlands category C (secondary obstetric care). NICE also lists “atypical antibodies which carry a risk of haemolytic disease of the newborn” as indicating birth in an obstetrical unit. The coverage guidance has been revised to include “Blood group incompatibility with atypical antibodies, or Rh sensitization” as a high risk coverage exclusion criterion for hospital birth to align with NICE.	45
K	5	As a trained healthcare provider myself, I see great potential in allowing women a better spectrum of choices in their prenatal and birthing experience. From firsthand experience, my care has been infinitely better and more comprehensive with a team of midwives versus a trained OB. For one, a typical OB visit is 15 minutes and they don't have the time or availability to provide holistic care to their clients. Their agenda is compressed into a "one-size-fits-all/most" model of the pregnancy process and they miss much opportunity to address specific points or concerns related to the individual woman. Consequently, if problems arise (even minor ones),	Thank you for your comments.	NA

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		the OB is forced to be reactive to the situation rather than proactive before the issue arises.		
K	6	With a midwife as the trained provider, the average prenatal visit is one hour, and each visit is tailored to the individual woman and her pregnancy experience. In-depth discussions are focused on things like diet, rest and exercise, new or ongoing stressors in the mother-to-be's life, etc. and all of which may have a direct impact on the pregnancy and/or birthing experience. More time is also afforded to discuss various treatment plans and options that relate to the individual woman and her preferences. Skilled midwives, therefore, have more of an ability to be proactive in a woman's care and to address potential risks before they start or get out of hand. In this sense, having a trained midwife can be viewed as choosing a more prophylactic route to a positive pregnancy and birth outcome.	Thank you for your comments.	NA
K	7	A skilled midwife, like a skilled OB, will have the client's best interest in mind, and will transfer care to a more skilled group if the situation necessitates. Just like an OB may transfer care of a high-risk patient to a more skillfully trained OB or specialist, or refer a woman to a more acute facility (Hospital instead of a birthing facility, or higher level hospital instead of community hospital), a midwife also has the ability and duty to refer a client to a more skilled professional or facility if the situation exceeds her scope of care. Autonomy should not be stripped from a trained and skilled provider. I think the stringency of the guidelines in the proposal should be modified so that trained and licensed midwives can still practice within the scope of what they were trained. Even VBAC's and Breach births can have healthy and safe outcomes at home if attended by a skilled midwife. And sometimes less intervention is more as far as quality of care and outcome.	See comment C1.	NA
L	1	I am not sure if or how this information will be of use to you, but HERC should know these things. **The HERC draft greatly understates the mortality difference between planned**	It is true, as the commenter states, that the data we cite may group pre-labor fetal death with intrapartum death and that some hospital deliveries where there was pre-labor fetal death may have been originally planned as out-of-hospital births. However, it is	NA

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		hospital births and planned out-of-hospital (OOH) births in Oregon in 2012. The report on 2012 Oregon births by planned birth place (1) and HERC draft both say that "The term perinatal mortality rate for planned OOH birth (4.0/1,000 pregnancies) was nearly twice that of in-hospital births (2.1/1,000)" (1). That is true, but the comparison is misleading because the perinatal mortality rate for planned hospital births included an unknown but relatively large number of antepartum (AP) fetal deaths that occurred *before* the mother was in labor. Eighty-five to 90 percent of all fetal deaths in developed countries are *stillbirths prior to labor* (2), and the incidence increases with gestational age (3) and thus is highest among term births. Most women whose babies die before labor go to a hospital to have labor induced and deliver their dead fetus in the hospital. In contrast to antepartum fetal deaths, intrapartum (IP) fetal deaths *during labor* are very rare in hospitals in developed countries, *only about 1 per 10,000* births (4). There were no intrapartum fetal deaths in a prospective 1980s study of almost 35,000 hospital births using either selective (for high-risk pregnancies) or universal electronic fetal monitoring (5). Antepartum fetal deaths comprise the vast majority of all fetal deaths that occur in American hospitals. Fifty-eight term fetal deaths were *associated with* 39,990 planned hospital births in Oregon in 2012 (1). We don't know how many were IP, but it is highly unlikely that more than six fetal deaths occurred during labor in Oregon hospitals that year. Four intrapartum fetal deaths were associated with planned OOH births in Oregon in 2012. All four were investigated by a public health pediatrician; all of them were intrapartum. It is misleading to compare a perinatal mortality rate that included an unknown but relatively high proportion of the 58 term fetal deaths associated with nearly 40,000 planned hospital births in Oregon in 2012 with the perinatal mortality rate for planned 2,021 planned OOH births, which included 4 early neonatal deaths and 4 intrapartum fetal deaths but no antenatal fetal deaths.	also true that chart review of the eight term fetal deaths and early neonatal deaths from the Oregon birth study shows that six of these deaths would not have met the criteria for coverage as outlined in this coverage guidance. The 2012 Oregon mortality rate, when adjusted for risk factors that should have excluded women from attempting OOH birth (and which this coverage guidance does not support) lies within the range of rates seen in the international and U.S. literature for both OOH and low-risk hospital births.	

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L	2	**The draft Guidance does not address the educational qualifications of home-birth attendants in Oregon.** The reviewed evidence is based primarily on studies from the Netherlands, Ontario and British Columbia. *All* midwives who attend home births in those jurisdictions are educated to the standards in the International Confederation of Midwives (ICM) Definition of the Midwife (6) and Global Standards for Basic Midwifery Education (7), as are all certified nurse-midwives (CNMs) in the United States (US). ICM defines a "midwife" in part as a person who has completed a three-year midwifery education program, or 18 months for students who enter as nurses or other healthcare professionals (6,7). In contrast to home births in those jurisdictions, most OOH births in Oregon are attended by direct entry midwives (DEMs), naturopaths and others with less midwifery education. In 2012, 62 percent of all planned out-of-hospital (OOH) births were attended by DEMs, 25 percent by CNMs, 11 percent by naturopaths (1). DEMs are limited to OOH births. Although some are knowledgeable and competent, some aren't; very few have completed a midwifery curriculum that meets ICM standards. Most, including certified professional midwives (CPMs), are trained through apprenticeship and self-study (8,9). Most naturopaths who attend births in Oregon graduated from the National College of Naturopathic Medicine (NCNM) in Portland. One three-credit lecture course in natural childbirth is part of the curriculum for all naturopathic physicians (10). NCNM also offers four three-credit lecture courses, one each on pregnancy, labor and birth, the postpartum period, and neonatology. Films are used to enhance lectures on techniques for monitoring the fetal/maternal condition and progress of labor, complications of labor and birth are discussed and skills needed to respond to them are demonstrated. Although NCNM does not provide any supervised clinical experience with pregnant women (10), to be licensed in Oregon naturopaths must have observed and assisted in 50 births supervised by a naturopath or obstetrician, pass a test and complete 15 hours of continuing education every year (11).	Thank you for your comment and information. Oregon law allows practice by midwives and other providers who do not have ICM standards of education. The draft guidance states "Certification requirements for the practice of midwifery vary significantly between the US and other countries, with US requirements being less rigorous with regard to both years of formal education and experience. See also comment F6. Box language requires home birth providers to be certified and licensed.	NA

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ID	#	Comment	Disposition	High-Risk Table Line
		CNMs attended only 25 percent of all planned OOH births in Oregon in 2012. All CNMs are educated to ICM standards in masters' degree programs, including one at OHSU. The IP fetal death rates from studies of home births attended by midwives who meet ICM education standards were zero in the small study from British Columbia, 0.31/1000 births in the very large study from the Netherlands, 0.45 in Ontario, and 0.36/1000 in England (12,13). In comparison the rate was 1.3 in a 2014 study of nearly 17,000 home births attended by members of the Midwives Alliance of North America (MANA) (14), four times higher than the mean rate if findings from all four of the ICM-education standard studies were combined. Eighty-five percent of births in the MANA study were attended by midwives who don't meet ICM education standards (15). The Ontario study reported total neonatal mortality (NN) instead of early NN mortality. ENN is preferable and was reported by the other three studies. The IP+NN rate for the Ontario study was 1.35/1000 births and 2.07/1000 for the MANA study. The IP+ENN mortality rates for the studies from British Columbia, the Netherlands and England were 0.35, 0.64 and 0.65 respectively. At 1.71/1000, the IP+ENN morality rate for the MANA study (14) was more than three times higher than the average for the studies based on births attended by midwives who meet ICM education standards. Intermittent auscultation is used to monitor the fetal heart rate in OOH births (15). It requires concentrated attention and a deep understanding of fetal heart rate changes and their significance during labor. Home birth midwives must be proficient in intermittent auscultation.		
L	3	HERC should add distance or time (not more than 30 minutes) from the home-birth residence to a hospital staffed and equipped to provide emergency care to a parturient woman or newborn to the criteria for coverage.	See comment E3.	NA
M	1	The Health Evidence Based Rules Commission (HERC) is in the process of developing Home Birth Draft Coverage Guidance defining low risk pregnancy that would be appropriate for planned home birth, as well as for maternal or pregnancy conditions	See comments D2, E1, E2, and G14.	

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ID	#	Comment	Disposition	High-Risk Table Line
		that would indicate the need for a higher level of prenatal, antenatal or postpartum care. Trillium Community health Plan would like to provide a list of additional guidelines to consider when drafting coverage guidance.		
		• Should complications occur at any point in the pregnancy, a re-evaluation should be performed to determine risk/status level.		15
		• Low risk characteristics should include an ultrasound between 12 – 30 weeks.		4
		• Low risk characteristics should include maternal and paternal age parameters such as 18 – 45 years of age.		7
		• Complications in a previous pregnancy should include third degree lacerations.		8
		• Complications of a previous pregnancy should include fractured clavicle and shoulder dystocia. (currently just shoulder dystocia)		10
		• Complications of a previous pregnancy should include history of large babies (>9 pounds).		13
		• Complications of current pregnancy should include having an IUD in place when becoming pregnant.		6
		• Complications of a current pregnancy should include parental Jehovah's Witness status – due to inability to transfuse.		11
		• Complications of current pregnancy vaginal delivery after C section.		3
		• Complications of a current pregnancy should include incomplete prenatal testing such as strep and all STDs.		15
		• Complications of a current pregnancy should include severe mental health issues not well controlled or addressed.		16
		• Transfer to a higher level of care considerations should include a transfer plan or protocol for DEMWs to include a transfer or back up plan for Obstetricians should be included.		38

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C2	Midwives' Association of Washington State INDICATIONS FOR DISCUSSION, CONSULTATION, AND TRANSFER OF CARE IN AN OUT-OF-HOSPITAL MIDWIFERY PRACTICE http://www.washingtonmidwives.org/documents/MAWS-indications-4.24.08.pdf
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Appendix 1

Midwives' Association of Washington State

INDICATIONS FOR DISCUSSION, CONSULTATION, AND TRANSFER OF CARE IN AN OUT-OF-HOSPITAL MIDWIFERY PRACTICE

2. DEFINITIONS:

2.1 DISCUSSION WITH ANOTHER MIDWIFE, AN ARNP, OR A PHYSICIAN

A discussion refers to a situation in which the midwife seeks advice or information from a colleague about a clinical situation, presenting her management plan for feedback.

2.1.1 It is the midwife's responsibility to initiate a discussion with and provide accurate and complete clinical information to another midwife, a nurse practitioner, or a physician in order to plan care appropriately. This discussion can take place between midwives in the same practice.

2.1.2 Discussion should occur in a timely manner soon after the clinical situation is discovered.

2.1.3 Discussion may occur in person, by phone, fax, or e-mail.

2.1.4 Discussion may include review of relevant patient records.

2.1.5 Discussion may include request for prescriptive medication based on signs or symptoms and/or laboratory results.

2.1.6 Discussion should be documented by the midwife in her records. Documentation of discussion should refer only to practitioner type without specifying the name of the practitioner contacted. Documentation should also include the midwife's management plan.

2.1.7 Discussion need not occur if the midwife has previously encountered a particular situation, discussed it with a colleague, developed a management plan, and is currently managing the same clinical presentation. In this case, documentation of the management plan and discussion with the client of the management plan is sufficient.

2.2 CONSULTATION WITH A PHYSICIAN

A consultation refers to a situation in which the midwife, using her professional knowledge of the client and in accordance with this document, or by client request, seeks the opinion of a physician competent to give advice in the relevant field. The consultant will either conduct an in-person assessment of the client or will evaluate the client's records in order to address the problem that led to the consultation.

2.2.1 It is the midwife's responsibility to initiate a consultation and to communicate clearly to the consultant that she is seeking a consultation.

2.2.2 A consultation can involve the physician providing advice and information, and/or providing care to the woman/newborn, and/or prescribing treatment for the woman or newborn.
2.2.3 In the case of an in-person consultation, the midwife should expect that the consultant will promptly communicate findings and recommendations to the client and the referring midwife after the consultation has taken place.
2.2.4 Where urgency, distance, or climatic conditions do not allow an in-person consultation with a physician when it would otherwise be appropriate, the midwife should seek advice from the physician by phone or other similar means. The midwife should document this request for advice in her records and discuss the consultant's advice with the client.
2.2.5 It is the midwife's responsibility to provide all relevant medical records to the consultant, including a written summary of the client's history and presenting problem, as appropriate.
2.2.6 Consultation must be fully documented by the midwife in her records, including the consultant's name, date of referral, and the consultant's findings, opinions, and recommendations. The midwife must then discuss the consultant's recommendations with the client.
2.2.7 After consultation with a physician, care of the client and responsibility for decision making, with the informed consent of the client, either continues with the midwife, is shared collaboratively by the midwife and the consultant, or transfers completely to the consultant. Transfer or sharing of care should occur only after dialogue and agreement among the client, the midwife, and the consultant.

2.3 TRANSFER TO A PHYSICIAN OR OTHER QUALIFIED HOSPITAL-BASED PROVIDER
When care is transferred permanently or temporarily from the midwife to a qualified hospital based provider, the receiving practitioner assumes full responsibility for subsequent decision making, together with the client. For guidance about intrapartum transfers, see also the MAWS document Planned Out-of-Hospital Birth Transport Guideline.

3.1 PRE-EXISTING CONDITIONS AND INITIAL HISTORY
Discussion:

- family history of significant genetic disorders, hereditary disease, or congenital anomalies
- history of pre-term birth (< 36 weeks)
- history of IUGR
- history of severe postpartum hemorrhage
- history of severe pre-eclampsia
- history of gestational diabetes

Consultation:

- history of uterine surgery, including: myomectomy, hysterotomy, or prior cesarean birth
- current or significant history of cardiovascular disease, renal disease, hepatic disorders, neurological disorders, severe gastrointestinal disease

- current or significant history of endocrine disorders (excluding controlled mild hypothyroidism)
- pulmonary disease/active tuberculosis/asthma if severe
- collagen-vascular diseases
- significant hematological disorders
- current or significant history of cancer
- history of cervical cerclage
- history of 3 consecutive spontaneous abortions
- significant uterine anomalies
- essential hypertension
- history of eclampsia or HELLP
- previous unexplained neonatal mortality or stillbirth
- isoimmunization with an antibody known to cause hemolytic disease of the newborn
- history of postpartum hemorrhage requiring transfusion
- current severe psychiatric illness
- no prenatal care prior to third trimester
- current or history of epilepsy

Transfer:

- absent prenatal care at term
- any serious medical condition, for example: cardiac disease, renal disease with failure, insulin-dependent diabetes mellitus, or uncontrolled asthma

3.2 ANTEPARTUM CONDITIONS

Discussion:

- urinary tract infection unresponsive to treatment
- significant abnormal ultrasound finding
- well-controlled gestational diabetes
- persistent size/dates discrepancies

Consultation:

- significant abnormal Pap
- significant abnormal breast lump
- pyelonephritis
- ectopic pregnancy

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- molar pregnancy
- thrombosis
- fetal demise after 14 weeks gestation
- persistent anemia, unresponsive to treatment
- primary herpes infection
- significant vaginal bleeding
- premature pre-labor rupture of membranes (PPROM)
- isoimmunization, hemoglobinopathies
- persistent abnormal fetal heart rate or rhythm
- significant placental abnormalities
- documented intrauterine growth restriction
- unresolved polyhydramnios or oligohydramnios
- significant infection the treatment of which is beyond the midwife's scope of practice
- 42 completed weeks with reassuring fetal surveillance
- presentation other than cephalic at 37 weeks

Transfer:

- multiple gestation
- persistent transverse lie, oblique lie, or breech presentation
- persistent hypertension, HELLP, pre-eclampsia, or eclampsia
- placenta previa at term
- clinically significant placental abruption
- cardiac or renal disease with failure
- uncontrolled gestational diabetes
- known fetal anomaly or condition that requires physician management during or immediately after delivery

3.3 INTRAPARTUM CONDITIONS

In certain intrapartum situations, the midwife may need to act immediately and transport may not be the most prudent course of action in that moment. It is expected that the midwife will use her clinical judgment and expertise in such situations, access 9-1-1 if appropriate, and then transport if and when it becomes necessary.

Discussion:

- arrested active phase of labor (>6 hours of regular, strong contractions without any significant change in cervix and/or station and/or position)
- arrested 2nd stage of labor (>3 hours of active pushing without any significant change)

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- prolonged rupture of membranes (>48 hours)

Transfer:

- labor before 37 weeks
- transverse lie, oblique lie, or breech presentation
- multiple gestation
- sustained maternal fever (>100.4 F) or other evidence of maternal infection
- moderate or thick meconium
- persistent non-reassuring fetal heart rate pattern
- maternal exhaustion unresponsive to rest/hydration
- abnormal bleeding during labor
- suspected placental abruption
- suspected uterine rupture
- persistent hypertension
- pre-eclampsia
- maternal seizure
- ROM >72 hours or ROM >18 hours with unknown GBS status and no prophylactic antibiotics or GBS+ and no prophylactic antibiotics
- prolapsed cord or cord presentation
- significant allergic response
- active genital herpes in vaginal, perineal or vulvar area in labor or after ROM
- client's clear desire for pain relief or hospital transport

3.4 POSTPARTUM CONDITIONS

Discussion:

- urinary tract infection unresponsive to treatment
- mastitis unresponsive to treatment
- subinvolution

Consultation:

- breast abscess
- retained products/unresolved subinvolution
- sustained hypertension
- significant abnormal Pap
- postpartum depression

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Transfer:

- significant postpartum hemorrhage unresponsive to treatment, with or without sustained maternal vital sign instability or shock
- retained placenta (>1 hour or active bleeding and manual removal unsuccessful)
- lacerations beyond midwife's ability to repair
- unusual or unexplained significant pain or dyspnea
- significant hematoma
- endometritis
- postpartum psychosis
- maternal seizure
- anaphylaxis
- persistent uterine prolapse or inversion

3.5 NEWBORN CONDITIONS

It is strongly recommended that all newborns be seen by an appropriate pediatric provider by 2 weeks of age. The following conditions warrant contact sooner.

Discussion:

- low birth weight infant (< 2500 gm = 5 lbs 8 oz)
- loss of greater than 10% of birth weight

Consultation:

- persistent cardiac arrhythmias or murmurs
- significant clinical evidence of prematurity
- failure to thrive
- hypoglycemia
- significant jaundice in first 24 hours or pathologic jaundice at any time

Transfer:

- seizure
- persistent respiratory distress
- persistent central cyanosis or pallor
- persistent temperature instability
- persistent hypoglycemia
- Apgar score less than 7 at five minutes of age and not improving
- major apparent congenital anomalies
- birth injury requiring medical attention

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Value-based Benefits Subcommittee Coverage Guidance Summary

Oregon Health Evidence Review Commission

October1, 2015

Oregon Health Authority

OREGON HEALTH & SCIENCE UNIVERSITY

Center For Evidence-based Policy

Coverage Guidance

For VbBS review and approval

- Proton Beam Therapy

Proton Beam Therapy
Process Overview

- Evidence Search (Jan 2015)
- HTAS – 2/2015, 6/2015, 9/2015
- Expert Testimony
- Extensive Public Comment (24 commenters)

Proton Beam Therapy
Primary Evidence Sources

Washington State Health Care Authority Health Technology Assessment Program. (2014). Proton Beam Therapy. Olympia, WA: Health Technology Assessment Program. Retrieved January 22, 2015 from http://www.hca.wa.gov/hta/Pages/proton.aspx.

Proton Beam Therapy
Clinical Background

- Protons – positively charged subatomic particles
- Proton beams – deposit radiation energy at or around target at the end of beam range
  - No exit dose radiation
- Treatment types
  - Primary treatment – curative intent
  - Recurrent disease – salvage treatment

Proton Beam Therapy
Clinical Background

Included cancerous conditions

- Bone tumors
- Brain, spinal, and paraspinal tumors
- Breast cancer
- Esophageal cancer
- Gastrointestinal cancers
- Gynecologic cancers
- Head and neck cancers (including skull base tumors)
- Liver cancer
- Lung cancer
- Lymphomas
- Ocular tumors
- Pediatric cancers (e.g., medulloblastoma, retinoblastoma, Ewing's sarcoma)
- Prostate cancer
- Soft tissue sarcoma
- Seminoma
- Thymoma

Included non-cancerous conditions

- Arteriovenous malformations
- Hemangiomas
- Other benign tumors (e.g., acoustic neuromas, pituitary adnomas

Proton Beam Therapy
Clinical Background

- Abbreviations
  - PBT – proton beam therapy
  - IMRT – intensity modulated radiation therapy
  - 3D-CRT – three dimensional conventional radiation therapy
  - DFS – disease-free survival
  - PFS – progression free survival
  - OS – overall survival
  - HR – hazard ratio

Proton Beam Therapy
Bone Cancer

Study Design (n, quality)	Specific Condition	Comparator	Outcome(s)
Curative, Salvage, Harms			
1 retrospective cohort (n=27, poor)	Primary and recurrent sacral chordomas	PBT + surgery vs PBT alone	Curative: >90% DFS (n=14) vs 50% survival (n=2) at 5 years Salvage: 42% survival (n=7) vs 50% survival (n=4) at 4-10 years Harms: lower rates of abnormal bowel or bladder function in PBT alone group

Proton Beam Therapy
Brain, Spinal, and Paraspinal Tumors

Study Design (n, quality)	Specific Condition	Comparator	Outcome(s)
Curative			
1 retrospective cohort study (n=40, poor)	Medulloblas-toma	PBT vs photon	No stat. difference in OS or PFS at 2 years
1 retrospective cohort study of (n=32, poor)	Intramedullary gliomas	PBT vs IMRT	PBT associated with increased mortality risk (HR 40.0, p=0.02)
Harms			
1 retrospective cohort study (n=40, poor)	Medulloblas-toma	PBT vs photon	PBT had lower rates of weight loss, medical management of esophagitis, nausea

Proton Beam Therapy
Esophageal Cancer

Study Design (n, quality)	Specific Condition	Comparator	Outcome(s)
Harms			
1 retrospective cohort (n=444, fair)	Esophageal cancer	Chemotherapy + (PBT vs IMRT vs 3D-CRT) + surgery	60 day follow-up: 3D-CRT vs PBT – high rates of post-operative pulmonary complications in 3D-CRT PBT vs IMRT – no diff
1 comparative study (n=75, fair)	Esophageal cancer	PBT vs IMRT vs 3D-CRT	Rate of pneumonitis high in PBT at 75 days

Proton Beam Therapy
Head and Neck Cancers

Study Design (n, quality)	Specific Condition	Comparator	Outcome(s)
Curative, Salvage*			
1 retrospective cohort of (n=33, poor)	Head and neck cancer	PBT vs PBT + photon	Curative: PBT + photon showed greater local control, reduced recurrence, mortality (not stat. tested) Salvage: PBT (n=3) vs PBT + photon (n=1)

* 1 add'l retrospective cohort of head and neck cancer (PBT vs IMRT, poorly described, n=6, poor-quality)

Proton Beam Therapy
Head and Neck Cancers

Study Design (n, quality)	Specific Condition	Comparator	Outcome(s)
Harms			
1 retrospective cohort of (n=33, poor)	Head and neck cancer	PBT vs PBT + photon	Toxicity rates ~ 22.8% at 3 and 5 yrs, not broken down by treatment
1 retrospective cohort of (n=75, fair)	Head and neck or skull base tumors	PBT vs carbon ion	No stat diff in radiation-induced optic neuropathy
1 retrospective cohort of (n=59, poor)	Head and neck or skull base tumors	PBT vs carbon ion	Lower rates of brain injury in PBT group (no stat test)

Proton Beam Therapy
Liver Cancer

Study Design (n, quality)	Specific Condition	Comparator	Outcome(s)
Curative			
1 prospective cohort study (n=35, fair)	Unresectable heptocellular carcinoma (HCC)	PBT vs PBT+chemo	Similar local tumor control rates
1 prospective cohort study (n=350, fair)	Unresectable heptocellular carcinoma (HCC)	PCT vs carbon ion	No diff in local control, OS

Proton Beam Therapy
Liver Cancer

Study Design (n, quality)	Specific Condition	Comparator	Outcome(s)
Salvage			
1 cohort study (n=8, poor)	Recurrent HCC after hepatectomy	PCT vs photon	No diff in local control
1 prospective cohort study (n=350, fair)	Unresectable heptocellular carcinoma (HCC)	PCT vs carbon ion	No diff in local control, OS

Proton Beam Therapy
Liver Cancer

Study Design (n, quality)	Specific Condition	Comparator	Outcome(s)
Harms			
1 cohort study of (n=8, poor)	Recurrent HCC after hepatectomy	PCT vs photon	No bone marrow depression or GI complications in either group; serum aspartate aminotransferase levels increased in all but 1 pt
1 prospective cohort study (n=350, fair)	Unresectable heptocellular carcinoma (HCC)	PCT vs carbon ion	Similar rates of toxicity

Proton Beam Therapy
Lung Cancer

Study Design (n, quality)	Specific Condition	Comparator	Outcome(s)
Curative			
1 retrospective cohort study (n=250, fair)	NSMLC	PBT vs IMRT	PBT had better lung function at 5-8 months (p=0.009)
1 prospective cohort study (n=202, fair)	Unresectable NSCLC	PBT vs IMRT or 3D-CRT	PBT had better OS though not significant (p=0.1061)
1 prospective cohort study (n=111, fair)	Lung cancer	PBT vs carbon ion	No diff in 3-year estimates of local control, PFS, OS

Proton Beam Therapy
Lung Cancer

Study Design (n, quality)	Specific Condition	Comparator	Outcome(s)
Salvage			
1 prospective cohort study (n=202, fair)	NSCLC	PBT vs IMRT or 3D-CRT	22% identified a having a prior malignancy of any type. Effects of prior malignancy not reported.
Harms			
1 prospective cohort study (n=652)	NSCLC	PBT vs IMRT vs 3D-CRT	Rates of esophagitis were higher in IMRT ($p<0.05$)

Proton Beam Therapy
Lung Cancer

Study Design (n, quality)	Specific Condition	Comparator	Outcome(s)
Harms			
1 prospective cohort study (n=202, fair)	Unresectable NSCLC	PBT vs IMRT or 3D-CRT	No diff in hematologic toxicity; PBT had lower rates of esophagitis and pneumonitis ($p<0.001$) and higher rates of dermatitis ($p<0.001$)
1 prospective cohort study (n=111, fair)	Lung cancer	PBT vs carbon ion	No diff in pneumonitis, dermatitis, rib fracture

Proton Beam Therapy
Ocular Tumors

Study Design (n, quality)	Specific Condition	Comparator	Outcome(s)
Curative			
1 RCT (n=151)	Uveal melanoma	PBT vs PBT + transpupillary thermotherapy	PBT had higher rate of secondary enucleation (p=0.02)
1 case series comparison to the RCT above (poor)	Uveal melanoma	PBT+ endoresection vs PBT vs PBT+ transpupillary thermotherapy	PBT+endoresection had lower rates of neovascular glaucoma

Proton Beam Therapy
Ocular Tumors

Study Design (n, quality)	Specific Condition	Comparator	Outcome(s)
Curative			
1 prospective cohort study (n=1,051, fair)	Uveal melanoma	PBT vs surgical enucleation	PBT had better OS at 2-5 years and lower rates of cancer-related death at two years
1 prospective cohort study (n=67, fair)	Uveal melanoma	PBT vs surgical enucleation	PBT had 50% metastasis-free survival rate at 5-years
1 prospective cohort studies (n=132, fair)	Uveal melanoma	PBT vs surgical enucleation	No diff in survival rates

Proton Beam Therapy
Ocular Tumors

Study Design (n, quality)	Specific Condition	Comparator	Outcome(s)
Curative			
1 prospective cohort study (n=88, fair)	Uveal melanoma	PBT vs PBT+chemo	No diff in OS at 5-8 years
1 noncontem-poraneous case series (n=56, poor)	Choroidal melanoma	PBT vs PBT+laser photocoag-ulation	No diff in visual acuity at 1 year

Proton Beam Therapy
Ocular Tumors

Study Design (n, quality)	Specific Condition	Comparator	Outcome(s)
Salvage			
1 comparative cohort study (n=73, fair)	Recurrent uveal melanoma after initial course of PBT	PBT vs surgical enucleation	PBT had higher OS at 5 years (p=0.04) and higher probability of being metastasis-free (p=0.028)

Proton Beam Therapy
Ocular Tumors

Study Design (n, quality)	Specific Condition	Comparator	Outcome(s)
Harms			
1 RCT (n=151)	Uveal melanoma	PBT vs PBT + transpupillary thermotherapy	No diff in cataracts, maculopathy, papillopathy, glaucoma or intraocular pressure. PBT+TTT lower rate of secondary enucleation (p=0.01)
1 prospective cohort study (n=132, fair)	Uveal melanoma	PBT vs surgical enucleation	Eye loss among PBT estimated at 26% at 5 years

Proton Beam Therapy
Pediatric Cancers

- Harms
  - Comparative studies are lacking, most likely due to a lack of clinical equipoise
  - Other than one study of secondary malignancy, no comparative studies of the harms of PBT in patients with pediatric cancers were identified
  - PBT's theoretical potential to lower radiation-induced toxicity in children serves as the comparative evidence base

Proton Beam Therapy
Prostate Cancer

Study Design (n, quality)	Specific Condition	Comparator	Outcome(s)
Curative			
1 RCT (n=202, fair)	Advanced prostate cancer	PBT+photon vs photon	No diff in local tumor control and OS at 5-years and 8-years In patients with poorly differentiated tumors, local control was better in PBT+photon at 8 years (p=0.0014)

Proton Beam Therapy
Prostate Cancer

Study Design (n, quality)	Specific Condition	Comparator	Outcome(s)
Curative			
1 prospective cohort study (n=185, fair)	Localized prostate cancer	PBT vs PBT+photon vs photon vs surgery vs watchful waiting	No diff in QoL or general health status at 18 months PBT alone had better physical function compared to surgery (p=0.01) or photon (p=0.02)
1 noncontem-poraneous case series (n=141, fair)	Prostate cancer	High-dose PBT+photon vs brachyltherapy	No diff in OS and freedom from metastasis at 8 years; brachyltherapy had higher proportion achieving nadir PSA level >=0.5 ng/ml (p<0.001)

Proton Beam Therapy
Prostate Cancer

Study Design (n, quality)	Specific Condition	Comparator	Outcome(s)
Curative			
1 comparison cohort study (n=206, poor)	Prostate cancer	Brachyltherapy vs PBT+photon	No diff in DFS after 5 years
1 comparison cohort study (poor)	Prostate cancer	PBT (n=95) vs IMRT (n=153) vs 3D-CRT (n=123)	No diff in bowel or urinary QoL
1 comparison case series (poor)	Prostate cancer	PBT (n=1,243) vs IMRT (n=204)	No diff in bowel, urinary, and sexual QoL at 2 years

Proton Beam Therapy
Prostate Cancer

Study Design (n, quality)	Specific Condition	Comparator	Outcome(s)
Harms			
1 RCT (n=202, fair)	Advanced prostate cancer	PBT+photon vs photon	Rectal bleeding higher in PBT+photon (p=0.002) No diff in rate of urethral stricture, hematuria, incontinence, and loss of potency
1 retrospective comparison study	Early stage prostate cancer	PBT (n=314) vs IMRT (n=628)	Rate of genitourinary toxicity were lower in PBT (p=0.03) at 6 months, but no diff at 12 months

Proton Beam Therapy
Prostate Cancer

Study Design (n, quality)	Specific Condition	Comparator	Outcome(s)
Harms			
1 matched cohort study	Prostate cancer	PBT (n=684) vs IMRT (n=684)	IMRT had lower rate of GI morbidity ($p<0.05$)
1 retrospective cohort study (n=30,000)	Prostate cancer	PBT vs IMRT vs 3D-CRT vs brachytherapy vs conservative management	All forms of radiation had higher rates of FI morbidity than conservative management

Proton Beam Therapy
Ocular Hemangiomas

Study Design (n, quality)	Specific Condition	Comparator	Outcome(s)
Curative			
1 retrospective cohort study (n=44, poor)	Diffuse or circumscribed hemangiomas	PBT vs photon	No diff on stabilization of visual acuity
Harms			
1 retrospective cohort study (n=44, poor)	Diffuse or circumscribed hemangiomas	PBT vs photon	Small differences were not statistically significant

Proton Beam Therapy
Other Benign Tumors

Study Design (n, quality)	Specific Condition	Comparator	Outcome(s)
Curative			
1 retrospective cohort study (n=20, poor)	Giant-cell bone tumors	PBT+photon vs photon	Similar outcomes between groups
1 cohort study (n=25, poor)	Optic nerve sheath meningioma	PBT vs photon vs PBT+photon	Visual acuity improved in most patients, with no diff among groups

Proton Beam Therapy
Other Benign Tumors

Study Design (n, quality)	Specific Condition	Comparator	Outcome(s)
Salvage			
1 Retrospective cohort (n=20, poor)	Giant-cell bone tumors	PBT+photon vs photon	5/20 with recurrent disease
Harms			
1 Cohort (n=25, poor)	Optic nerve sheath meningioma	PBT vs photon vs PBT+photon	PBT and PBT+photon: lower rates of acute orbital pain and higher rates of late asym. Retinopathy (not stat. tested)

Proton Beam Therapy
Public Comment Summary

- Comment received in support of PBT for
  - Brain, spinal, and paraspinal tumors
  - Breast cancer
  - Gastrointestinal cancers
  - Head and neck cancers (including skull base tumors)
  - Liver cancer
  - Lung cancer
  - Lymphomas
  - Pediatric cancers (e.g., medulloblastoma, reinoblastoma, Ewing's sarcoma)
  - Prostate cancer

Proton Beam Therapy
Core issues raised by expert/public

- Recurrent cancers
- Definition of pediatric
- Longevity of benefit (children, lymphomas)
- Coverage with evidence development
- Noncomparative studies
- Dosimetric modeling
- Relative costs

Proton Beam Therapy
Box Language

- *Please refer to Coverage Guidance for*
  - *Box language*
  - *GRADE table*

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: PROTON BEAM THERAPY

DRAFT for VbBS/HERC meeting materials 11/12/2015

HERC Coverage Guidance

Proton beam therapy (PBT) is recommended for coverage for malignant ocular tumors (*strong recommendation*).

Proton beam therapy is recommended for coverage *(weak recommendation)* for:

- malignant brain, spinal, skull base, paranasal sinus, and juxtaspinal tumors
- pediatric malignant tumors (incident cancer under age 21)

Proton beam therapy is not recommended for coverage for cancer of the bone, breast, oropharynx, nasopharynx, esophagus, liver, lung, or prostate or for gynecologic or gastrointestinal cancers, lymphoma, sarcoma, thymoma, seminoma, arteriovenous malformation or ocular hemangiomas *(weak recommendation).*

Note: Definitions for strength of recommendation are provided in Appendix A GRADE Element Description

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Heath Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

EVIDENCE SOURCES

Trusted sources

Washington State Health Care Authority Health Technology Assessment Program. (2014). Proton Beam Therapy. Olympia, WA: Health Technology Assessment Program. Retrieved January 22, 2015 from http://www.hca.wa.gov/hta/Pages/proton.aspx.

DRAFT

The summary of evidence in this document is derived directly from this evidence source, and portions are extracted verbatim.

EVIDENCE OVERVIEW

Clinical background

Protons are positively-charged subatomic particles that have been in clinical use as a form of external beam radiotherapy for over 60 years. Compared to the photon X-ray energy used in conventional radiotherapy, proton beams have physical attributes that are potentially appealing. Specifically, protons deposit radiation energy at or around the target, at the end of the range of beam penetration, a phenomenon known as the Bragg peak. The goal of any external beam radiotherapy is to deliver sufficient radiation to the target tumor while mitigating the effects on adjacent normal tissue. This has been a challenge for conventional photon therapy due to the amount of radiation deposited both before and after the target is reached. While the amount of photon radiation at entry into the body is much higher than at exit, photon beams typically "scatter" to normal tissues after leaving the target. This so-called "exit" dose is absent for protons, as tissue beyond the point of peak energy deposition receives little to no radiation**.**

Initial use of proton beam therapy (PBT) focused on conditions where sparing very sensitive adjacent normal tissues was felt to be of utmost importance, such as cancers or noncancerous malformations of the brain stem, eye, or spinal cord. In addition, proton beam therapy was advocated for many pediatric tumors because even lower-dose irradiation of normal tissue in pediatric patients can result in pronounced acute and long-term toxicity. There are also long-standing concerns regarding radiation's potential to cause secondary malignancy later in life, particularly in those receiving radiation at younger ages. Finally, radiation may produce more nuanced effects in children, such as neurocognitive impairment in pediatric patients treated with radiotherapy for brain cancers.

More recently, however, the use of PBT has been expanded in many settings to treat more common cancers such as those of the prostate, breast, liver, and lung. With the growth in potential patient numbers and reimbursement, the construction of proton centers has grown substantially. There are now 14 operating proton centers in the U.S., including one in Seattle, WA that came online in March 2013. Eleven additional centers are under construction or in the planning stages, and many more are proposed. The construction of cyclotrons at the heart of proton beam facilities is very expensive ($150-$200 million for a multiple gantry facility).

Indications

This appraisal focuses on the use of proton beam therapy (PBT) to treat patients with multiple types of cancer as well as those with selected noncancerous conditions. Within each condition type, two general populations were specified as of interest for this evaluation**:**

- Patients receiving PBT as primary treatment for their condition (i.e., curative intent)
- Patients receiving PBT for recurrent disease or for failure of initial therapy (i.e., salvage)

All forms of PBT were considered for this evaluation, including monotherapy, use of PBT as a "boost" mechanism to conventional radiation therapy, and combination therapy with other

modalities such as chemotherapy and surgery. All PBT studies that met entry criteria for this review were included, regardless of manufacturer, treatment protocol, location, or other such concerns.

Conditions included in the evidence review are as follows:

- Cancers
- Bone tumors
- Brain, spinal, and paraspinal tumors
- Breast cancer
- Esophageal cancer
- Gastrointestinal cancers
- Gynecologic cancers
- Head and neck cancers (including skull base tumors)
- Liver cancer
- Lung cancer
- Lymphomas
- Ocular tumors
- Pediatric cancers (e.g., medulloblastoma, retinoblastoma, Ewing's sarcoma)
- Prostate cancer
- Soft tissue sarcomas
- Seminoma
- Thymoma
- Noncancerous Conditions
- Arteriovenous malformations
- Hemangiomas
- Other benign tumors (e.g., acoustic neuromas, pituitary adenomas)

Evidence review

A summary of the net health benefit of PBT vs. alternative treatments and the strength of available evidence on net health benefit, as well as an evaluation of consistency of these findings with clinical guideline statements and public/private coverage policy, can be found in Table 1. The level of comparative evidence was extremely limited for certain conditions and entirely absent for others. We identified a total of six RCTs and 37 nonrandomized comparative studies across all 19 condition types. Importantly, five of the six RCTs involved different treatment protocols for PBT and had no other comparison groups; while these are included for completeness, primary attention was paid to studies (RCTs and otherwise) that compared PBT to an alternative form of treatment.

Most of the comparative studies identified also had major quality concerns. For example, nearly all non-randomized comparative studies were retrospective in nature, and many involved comparisons of a PBT cohort to a non-contemporaneous group receiving alternative therapy. Major differences in patient demographics and baseline clinical characteristics as well as duration of follow-up were often noted between groups. Of the 6 RCTs identified, 1, 4, and 1

were judged to be of good, fair, and poor quality respectively. Corresponding figures for non-randomized comparative studies were 1, 20, and 16.

As noted on Table 1, PBT was judged to have superior net health benefit for ocular tumors, and incremental net health benefit for adult brain/spinal tumors and pediatric cancers. PBT was comparable to alternative treatment options for patients with liver, lung, and prostate cancer as well as one noncancerous condition (hemangiomas). Importantly, however, the strength of evidence was low for all of these conditions. The evidence base for all other condition types was insufficient to determine net health benefit, including two of the four most prevalent cancers in the U.S.: breast and gastrointestinal (lung and prostate are the other two).

As with information on clinical effectiveness, data on potential harms of PBT come from RCTs, comparative cohort studies, and case series, although comparative harms data are still lacking for many condition types. Across all condition types, a total of 25 studies reported comparative information on treatment-related harms; differences in the types of harms relevant to each condition, as well as variability in harms classification even within conditions, precludes any attempt to summarily present harms data across all 19 condition categories.

Observational data on secondary malignancy with PBT are generally lacking. Two studies were identified with comparative information. One was a fair-quality matched retrospective cohort study comparing 1,116 patients in a linked Medicare-SEER database who received either PBT or photon radiation for a variety of cancers and were followed for a median of 6.4 years. On an unadjusted basis, the incidence rates of any secondary malignancy and malignancies occurring in the prior radiation field were numerically lower for PBT, but not statistically-significantly so. After adjustment for age, sex, primary tumor site, duration of follow-up, and year of diagnosis, PBT was associated with a risk of secondary malignancy approximately one-half that of photon therapy (HR=0.52; 95% CI: 0.32, 0.85; p=0.009). There are challenges with these findings, however. First and foremost, the lower rate of secondary malignancy with PBT appeared to be manifested almost entirely in the first five years after radiotherapy, a time period in which a second cancer event is not typically attributed to prior radiation (Bekelman, 2013). In addition, patients were accrued over a very long time period (1973-2001), only the very end of which included highly conformal photon techniques like IMRT.

The second study was a poor-quality retrospective cohort study comparing PBT to photon radiotherapy in 86 infants who were treated for retinoblastoma and followed for a median of 7 years (PBT) or 13 years (photon radiotherapy). Therapy was received at two different US centers (PBT at MGH and photon radiotherapy at Children's Hospital Boston). Kaplan-Meier analyses were conducted to control for differential follow-up but no adjustments were made for other differences between groups. Ten-year estimates of the cumulative incidence of secondary malignancy were numerically lower for PBT, but not statistically significantly so (5% vs. 14% for photon, p=0.12). However, when malignancies were restricted to those occurring in-field or thought to be radiation-induced, a significant difference in favor of PBT was observed (0% vs. 14%, p=0.015). In addition, significant differences in favor of PBT in both cumulative incidence and radiotherapy-related malignancy were observed for the subgroup of patients with hereditary disease.

Other harms are presented in detail for each condition type in the sections that follow.

No comparative studies were identified for curative therapy of: breast, esophageal, gastrointestinal, gynecologic, and pediatric cancers; lymphomas, sarcomas, seminomas, and thymomas; arteriovenous malformations.

No comparative studies were identified for salvage treatment of: brain/spinal/paraspinal, breast, esophageal, gastrointestinal, gynecologic, pediatric, and prostate cancers; lymphomas, sarcomas, seminomas, and thymomas; arteriovenous malformations and hemangiomas.

No comparative studies of harms identified for: gastrointestinal and gynecologic cancers; lymphomas, sarcomas, seminomas, and thymomas; arteriovenous malformations.

Cancers

Bone Cancer

Curative

A single poor-quality retrospective comparative cohort study evaluated PBT for primary and recurrent sacral chordomas in 27 patients. Among these patients 21 were treated with surgery and combination PBT /photon therapy (mean radiation dose: 72.8 Gray Equivalents [GyE]), in comparison to six patients who received PBT/photons alone (mean dose: 70.6 GyE). For patients with primary tumors, Kaplan-Meier estimates of local control, disease-free survival and overall survival exceeded 90% among those treated by surgery and radiation (n=14). Only two of the six patients with primary tumors received radiation alone, one of whom had local failure at four years, distant metastases at five years, and died at 5.5 years.

Salvage

In the same study of 27 patients with sacral chordomas who were treated with PBT/photon radiation alone or in combination with surgery, seven radiation/surgery patients and four radiation-only patients had recurrent disease. Among patients in the radiation/surgery group, four patients died of disease 4-10 years after treatment; the remainder was alive with disease at last follow-up. In the radiation-only group, two of four patients died of disease at 4-5 years of follow-up; the other two were alive with disease at last follow-up.

Harms

In the study described above, multiple descriptive harms were reported. Patients receiving radiation alone reported numerically lower rates of abnormal bowel or bladder function as well as difficulty ambulating in comparison to those receiving combination therapy, but rates were not statistically tested. PBT patients also reported higher rates of return to work, although this was also not tested statistically. Evidence is thus inadequate to compare the potential harms of PBT relative to other radiation modalities in patients with bone cancer.

Brain, Spinal, and Paraspinal Tumors

Curative

Two poor-quality retrospective comparative cohort studies investigated primary PBT for brain, spinal, and paraspinal tumors. One was an evaluation of PBT (mean dose: 54.6 GyE) vs. photon therapy (mean dose: 52.9 Gy) in 40 adults (mean age: 32 years; 65% male) who received surgical and radiation treatment of medulloblastoma at a single US cancer center. PBT patients were followed for a median of 2.2 years, while photon patients were followed for a

median of nearly five years. No statistical differences between radiation modalities were seen in Kaplan-Meier assessment of either overall or progression-free survival at two years. A numeric difference was seen in the rate of local or regional failure (5% for PBT vs. 14% for photon), but this was not assessed statistically.

The second study involved 32 patients treated for intramedullary gliomas with either PBT (n=10) or IMRT (n=22). While explicit comparisons were made between groups, the PBT population was primarily pediatric (mean age: 14 years), while the IMRT population was adult (mean age: 44 years). Patients in both groups were followed for a median of 24 months; dose was >50 GyE or Gy in approximately 75% of patients. While the crude mortality rate was lower in the PBT group (20% vs. 32% for IMRT, not tested), in multivariate analyses controlling for age, tumor pathology, and treatment modality, PBT was associated with significantly increased mortality risk (Hazard Ratio [HR]: 40.0, p=0.02). The rate of brain metastasis was numerically higher in the PBT group (10% vs. 5% for IMRT), but this was not statistically tested. Rates of local or regional recurrence did not differ between groups.

Harms

In the first study described above, PBT was associated with statistically-significantly lower rates of weight loss (median % of baseline: -1.2% vs. 5.8% for photon, p=0.004) as well as requirements for medical management of esophagitis (5% vs. 57% respectively, p<0.001). PBT patients also experienced less RTOG grade 2 or greater nausea and vomiting (26% vs. 71%, p=0.004).

In the second study comparing primarily 10 pediatric patients (mean age: 14 years) receiving PBT for spinal cord gliomas to 22 adults receiving IMRT for the same condition (mean age: 44 years) (Kahn, 2011), no cases of long-term toxicity or myelopathy were reported in either group. Minor side-effect rates were reported for the overall cohort only. In summary, limited, low-quality evidence suggests that PBT is associated with reductions in acute radiation-related toxicity relative to photon radiation in patients with brain and spinal tumors.

Table 1: Summary table assessing strength of evidence, direction of benefit, and consistency with relevant guideline statements and coverage policy.

Condition	Incidence (per 100,000)	Net Health Benefit vs. Comparators	Type of Net Health Benefit	Strength of Evidence	Guideline Recommendations	Coverage Policies
Cancer						
Bone	1.3	Insufficient	---	+	M	M
Brain/spinal	9.6	Incremental	B: = H: ↓	+	U	U
Breast	97.7	Insufficient	---	o	NM	NR/NC
Esophageal	7.5	Insufficient	---	o	NM	NR/NC
GI	100.6	Insufficient	---	o	NM	NR/NC
Gynecologic	38.2	Insufficient	---	o	NM	NR/NC
Head/neck	17.2	Insufficient	---	+	NM	M
Liver	12.8	Comparable	B: = H: =	+	NM	M
Lung	95.0	Comparable	B: = H: =	+	M	M
Lymphomas	32.9	Insufficient	---	o	NR/NC	NR/NC
Ocular	1.2	Superior	B: ↑ H: ↓	++	U	U
Pediatric	9.1	Incremental	B: = H: ↓	+	U	U
Prostate	99.4	Comparable	B: = H: =	+	M	M
Sarcomas	4.8	Insufficient	---	o	NM	M
Seminoma	4.0	Insufficient	---	o	NM	NM
Thymoma	0.2	Insufficient	---	o	NM	NM
Noncancerous						
AVMs	1.0	Insufficient	---	o	NM	M
Hemangiomas	2.0	Comparable	B: = H: =	+	NM	NM
Other	2.0	Insufficient	---	o	NM	M

B: Benefits; H: Harms

Strength of Evidence: Low=+; Moderate=++; High=+++; No evidence=o

Legend: U = Universally recommended or covered; M=Mixed recommendations or coverage policies; NM=Not mentioned in guidelines or coverage policies; NR/NC=Not recommended or not covered

Esophageal Cancer

Harms

Two studies were identified that examined comparative harms in patients treated with PBT for esophageal cancer. One was a relatively large, fair-quality, retrospective comparative cohort study of 444 patients (median age: 61 years; 91% male) who were treated with chemotherapy and radiation (PBT, IMRT, or 3D-CRT) followed by surgical resection. Patients were followed for up to 60 days after hospital discharge. After adjustment for patient characteristics and clinical variables, 3D-CRT was associated with a significantly greater risk of postoperative pulmonary complications vs. PBT (Odds Ratio [OR]: 9.13, 95% CI: 1.83, 45.42). No significant differences were observed between PBT and IMRT, however. No differences in the rate of gastrointestinal complications were observed for any treatment comparison.

In addition, a fair-quality comparative study was identified that examined early impact on lung inflammation and irritation in 75 patients receiving PBT, IMRT, or 3D-CRT for esophageal cancer; patients were followed for up to 75 days following radiation. Nearly all outcome and toxicity measures were reported for the entire cohort only. However, the rate of pneumonitis was found to be significantly higher among PBT patients (33% vs. 15% for IMRT/3D-CRT, p=0.04). In summary, evidence is inadequate to compare the potential harms of PBT relative to other radiation modalities in patients with esophageal cancer, particularly in comparison to IMRT.

Head and Neck Cancers

Curative

There were two poor-quality retrospective comparative cohorts of primary PBT in head and neck cancer. One was an evaluation of 33 patients treated with either PBT alone or PBT+photon therapy to a target dose of 76 Gy for a variety of head and neck malignancies in Japan. Treatment groups differed substantially in terms of age, gender, and duration of follow-up (mean: 5.9 vs. 3.1 years). Numeric differences in favor of PBT+photon therapy were seen for local control, recurrence, and mortality, but these were not statistically tested, nor were multivariate adjustments made for differences between groups.

The other study was a very small (n=6) comparison of endoscopic resection followed by either PBT or IMRT as well as endoscopy alone in patients with malignant clival tumors. Limited description of the study suggests that PBT was used only in cases of residual disease, while it is unclear whether IMRT was also used in this manner or as an adjuvant modality. One of the IMRT patients died of causes unrelated to disease; no other deaths were reported.

Salvage

In the first study described above, four patients were identified as having recurrent disease, three of whom received PBT alone. Two of the three PBT-only patients were alive with local tumor control at last follow-up (5 and 17 years respectively); one patient had their cancer recur three months after PBT and died in month 7 of follow-up. The one PBT+photon patient died at 2.5 years of follow-up, but was described as having local tumor control.

Harms

In the first study describe above, rates of tongue ulceration, osteonecrosis, and esophageal stenosis differed somewhat between treatment groups, but were not statistically tested. Overall toxicity rates were estimated to be 22.8% at both three and five years, but were not stratified by treatment modality.

In a separate, fair-quality study comparing rates of vision loss from radiation-induced optic neuropathy in 75 patients treated with PBT or carbon-ion therapy for head and neck or skull base tumors, unadjusted rates of vision loss were similar between modalities (8% and 6% for PBT and carbon-ion respectively, not statistically tested). In multivariate analyses controlling for demographic and clinical characteristics, treatment modality had no effect on rates of vision loss (p=0.42). Another comparison of PBT and carbon-ion therapy in 59 patients with head and neck or skull base tumors was of poor quality (due to no control for differences between patient groups) and focused on the incidence of radiation-induced brain changes. The incidence of CTCAE brain injury of any grade was significantly (p=0.002) lower in the PBT group. MRI-based assessment of brain changes showed a lower rate in the PBT group (17% vs. 64% for carbon-ion), although this was not tested statistically. In summary, evidence is inadequate to compare the potential harms of PBT relative to other radiation modalities in patients with head and neck cancer.

Liver Cancer

Curative

Two fair-quality prospective comparative cohort studies provided evidence of the clinical effectiveness of primary use of PBT in liver cancer. One was an evaluation of 35 patients with unresectable hepatocellular carcinoma (HCC) who were treated with PBT (mean dose: 76.5 GyE) either alone or in combination with chemotherapy and were followed for up to 4 years. While statistical testing was not performed, rates of local tumor control and the proportion of patients experiencing reductions in tumor volume were nearly identical between groups.

The other study was also prospective but compared PBT to another heavy-ion modality not in circulation in the U.S. (carbon ion). In this study, a fair-quality comparison of 350 patients with HCC who received PBT (53-84 GyE) or carbon-ion (53-76 GyE) therapy and were followed for a median of 2.5 years, no statistically-significant differences were observed in 5-year Kaplan-Meier estimates of local control, no biological evidence of disease, or overall survival between treated groups.

Salvage

Two studies were identified with information on recurrent disease. One was a poor-quality comparison of PBT to conventional photon radiation in eight patients with recurrent HCC after hepatectomy. Five patients were treated with PBT (68.8-84.5 GyE), and three with photons (60-70 Gy). Seven of eight patients died of liver failure or lung metastasis a median of 1.5 years after radiation; the one patient alive at the end of follow-up was a photon patient. The rate of local tumor control was 78%, and did not differ between treatment groups.

The other study was a previously-described prospective comparison of PBT to carbon-ion therapy in 350 patients with primary or recurrent HCC. No subgroup analyses were performed, but prior treatment history for HCC was found not to have a statistically-significant impact on local tumor control (p=0.73). Prior treatment was not examined as a risk factor for overall survival, however.

Harms

Two comparative studies were identified with comparative information on radiation-related harms. In a previously-described study of eight patients with recurrent HCC after hepatectomy, there were no instances of bone marrow depression or gastrointestinal complications in either group. Serum aspartate aminotransferase (AST) levels increased in the three photon patients and 4/5 PBT patients, although this was not tested statistically.

In the other study, a previously-described comparison of PBT to carbon-ion therapy in 350 patients with primary or recurrent HCC, rates of toxicities as graded by the Common Terminology Criteria for Adverse Events (CTCAE) framework were comparable between groups, including dermatitis, GI ulcer, pneumonitis, and rib fracture. The rate of grade 3 or higher toxicities was similar between groups (3% vs. 4% for PBT and carbon-ion respectively), although this was not statistically tested.

In summary, limited, low-quality evidence suggests that PBT is associated with comparable rates of toxicity to other radiation modalities in patients with liver cancer.

Lung Cancer

Curative

Three fair-quality comparative cohort studies examined the clinical effectiveness of PBT in lung cancer. Two studies retrospectively compared outcomes with PBT to those with IMRT or older three-dimensional conformal radiotherapy (3D-CRT) at a US cancer center. One study involved 250 patients with non-small-cell lung cancer (NSCLC) who were treated with 66 Gy of photons or 74 GyE of protons and followed for up to one year to assess a key measure of lung function known as diffusing capacity of lung for carbon monoxide (DLCO). While this measure did not differ between PBT and IMRT at 5-8 months after treatment, DLCO declined significantly more in the 3D-CRT group as compared to PBT after adjustment for pretreatment characteristics and other lung function measures (p=0.009).

A second study focused on survival in 202 patients with locally-advanced, unresectable NSCLC who were followed for a median of 1.5 years and treated 74 GyE of PBT or 63 Gy of either IMRT or 3D-CRT. Actuarial estimates of median overall survival were 24.4, 17.6, and 17.7 months for PBT, IMRT, and 3D-CRT respectively, although these differences were not statistically significant (p=0.1061).

A third study was a prospectively-measured cohort but, as with the study of liver cancer mentioned above, compared PBT to carbon ion therapy, evaluating 111 Japanese NSCLC patients over a median of 3.5 years. No statistically-significant differences between groups were observed in three-year actuarial estimates of local control, progression-free survival, or overall survival.

Salvage

In the second study described above, 22% of the study sample was identified as having a prior malignancy of any type. The effects of prior malignancy on overall survival were not reported, however.

Harms

A total of three comparative studies assessed harms in patients with lung cancer. One was a study of severe radiation-induced esophagitis (within six months of treatment) among 652 patients treated for NSCLC with PBT, IMRT, or 3D-CRT at a US cancer center. Rates of grade 3 or higher esophagitis were 6%, 8%, and 28% for PBT, 3D-CRT, and IMRT respectively ($p<.05$ for PBT and 3D-CRT vs. IMRT).

In the previously-described noncontemporaneous case series comparison of patients with locally-advanced, unresectable NSCLC who were treated with PBT, IMRT, or 3D-CRT, hematologic toxicity rates did not differ by radiation modality. Significant differences in favor of PBT were seen in rates of grade 3 or higher esophagitis (5%, 39%, and 18% for PBT, IMRT, and 3D-CRT respectively, $p<0.001$) as well as pneumonitis (2%, 6%, and 30%, $p<0.001$), while rates of grade 3 or higher dermatitis were significantly greater in the PBT group (24% vs. 17% and 7% for IMRT and 3D-CRT, $p<0.001$).

Finally, in a previously-described comparison of PBT to carbon-ion therapy in 111 patients in Japan, rates of pneumonitis, dermatitis, and rib fracture did not differ statistically between radiation modalities across all toxicity grades. In summary, moderate evidence suggests that rates of treatment-related toxicities with PBT are comparable to those seen with other radiation modalities in patients with lung cancer.

Ocular Tumors

Curative

In comparison to other cancer types, the evidence base for ocular tumors was relatively substantial. A total of seven comparative studies were identified of the clinical benefits of primary PBT in such cancers—a single RCT, four retrospective cohort studies, a comparison of a recent case series to the treatment groups from the RCT, and a comparison of noncontemporaneous case series. The RCT compared PBT alone to a combination of PBT and transpupillary thermotherapy (TTT) in 151 patients treated for uveal melanoma and followed for a median of 3 years. Combination therapy was associated with a statistically-significantly ($p=0.02$) reduced likelihood of secondary enucleation; no other outcomes differed significantly between groups. In a separate, poor-quality comparison of these findings to a separate series of patients undergoing PBT with endoresection of the scar, rates of secondary enucleation did not differ between groups, but rates of neovascular glaucoma were significantly lower in the PBT+endoresection group vs. the groups from the RCT (7% vs. 58% and 49% for PBT alone and PBT+TTT respectively, $p<0.0001$). Of note, however, median follow-up was less than two years in the PBT+endoresection series vs. 9 years in the RCT.

Three of the cohort studies were all fair-quality and involved comparisons to surgical enucleation in patients with uveal melanoma at single centers. PBT was associated with statistically-significant improvements in overall survival rates relative to enucleation at 2-5 years in two of these studies. Rates of metastasis-related and all cancer-related death were statistically-significantly lower among PBT patients through two years of follow-up in one study (n=1,051), but were nonsignificant at later timepoints. The 5-year metastasis-free survival rate in a second study (n=67) was 50% higher among PBT patients in a Cox regression model controlling for baseline characteristics (59.0% vs. 39.4% for enucleation, p=0.02). In the third study, Kaplan-Meier curves for all-cause mortality, melanoma-related mortality and metastasis-free survival did not statistically differ for 132 patients treated with PBT and enucleation. Metastasis-free survival also did not differ in Cox regression adjusting for age, sex, and tumor thickness.

Another fair-quality study assessed the impact of PBT + chemotherapy vs. PBT alone in 88 patients with uveal melanoma who were followed for 5-8 years. Five-year overall survival rates did not statistically differ between groups on either an unadjusted or Cox regression-adjusted basis.

Finally, a poor-quality comparison of noncontemporaneous case series evaluated treatment with PBT + laser photocoagulation or PBT alone in 56 patients with choroidal melanoma. At one year, there were no differences in visual acuity between groups.

Salvage

A single comparative study examined PBT in recurrent ocular cancer. In this fair-quality, comparative cohort study, a total of 73 patients with uveal melanoma had recurrence of disease following an initial course of PBT at a US hospital. Patients (mean age: 58 years) were treated with either a second course of PBT (70 GyE) in five fractions or surgical enucleation and followed for 5-7 years. The likelihood of overall survival at five years was significantly (p=0.04) longer in the PBT group (63% vs. 36% for enucleation), as was the probability of being free of metastasis at this timepoint (66% vs. 31% respectively, p=0.028). Findings were similar after Cox proportional hazards regression adjusting for tumor volume and year of retreatment as well as patient age. The likelihood of local tumor recurrence at five years was 31% in the PBT group. No local recurrences were found in the enucleation group, which is not surprising given the nature of the treatment.

Harms

Two comparative studies assessed the harms of PBT for ocular cancers. In the previously-described RCT comparing PBT with thermotherapy to PBT alone in 151 patients with uveal melanoma, no statistically-significant differences were observed between groups in rates of cataracts, maculopathy, papillopathy, glaucoma, or intraocular pressure. The combination therapy group had a significantly lower rate of secondary enucleation (p=0.02), although actual figures were not reported.

In a previously-described comparison of PBT to enucleation in 132 patients treated for unilateral choroidal tumors, rates of eye loss in the PBT arm were assessed and estimated to be 26% at five years of follow-up. In summary, limited, low-quality evidence suggests comparable rates of harm for PBT relative to treatment alternatives in patients with ocular tumors.

Pediatric Cancers

Harms

PBT's theoretical potential to lower radiation-induced toxicity in children serves as the comparative evidence base. Comparative studies are lacking, most likely due to a lack of clinical equipoise.

Other than the study of secondary malignancy described above, no comparative studies of the potential harms of PBT in patients with pediatric cancers were identified.

Prostate Cancer

Curative

The largest evidence base available was for prostate cancer (10 studies). However, only 6 of these studies reported clinical outcomes *and* compared PBT to alternative treatments. These included an RCT, a prospective comparative cohort, and four comparisons of noncontemporaneous case series.

The included RCT was a fair-quality comparison of 202 patients with advanced (stages T3-T4) prostate cancer who were randomized to receive either photon therapy with a proton boost (total dose: 75.2 GyE) or photons alone (67.2 Gy) and were followed for a median of five years. Kaplan-Meier estimates of local tumor control, disease-specific survival, and overall survival were similar at both 5- and 8-year timepoints among the entire intent-to-treat population as well as those completing the trial (n=189). However, in patients with poorly-differentiated tumors (Gleason grades 4 or 5), local control at 8 years was significantly better in patients receiving PBT+photons (85% vs. 40% for photons alone, p=0.0014).

The prospective cohort study was a fair-quality comparison of patient-reported health-related QoL at multiple timepoints among 185 men (mean age: 69 years) with localized prostate cancer who were treated with PBT, PBT+photons, photons alone, surgery, or watchful waiting. Overall QoL, general health status, and treatment-related symptom scales were employed. No differences in overall QoL or general health status were observed at 18 months of follow-up, although men treated with PBT monotherapy reported better physical function in comparison to surgery (p=0.01) or photon radiation (p=0.02), and better emotional functioning in relation to photon radiation (p<0.001). Men receiving PBT+photons also reported significantly fewer urinary symptoms at 18 months in comparison to watchful waiting (p<0.01).

Outcomes were also assessed in three comparisons of noncontemporaneous case series. One was a fair-quality evaluation of high-dose PBT+photons (79.2 GyE) in 141 patients enrolled in a clinical trial who were matched on clinical and demographic criteria to 141 patients treated with brachytherapy. Patients were followed for a median of eight years. Eight-year actuarial estimates of overall survival, freedom from metastasis, and biochemical failure did not statistically differ between groups. The proportion of patients achieving a nadir PSA level of ≤0.5 ng/mL as of their final measurement was significantly higher in the brachytherapy group (92% vs. 74% for PBT, p=0.0003).

Two additional studies were deemed to be of poor quality due to a lack of control for confounding between study populations. One was a comparison of a cohort of 206 brachytherapy patients compared with the same PBT+photon group described above. The difference in the percentage of patients achieving nadir PSA after a median of 5.4 years of follow-up was similar to that reported in the study above (91% vs. 59%), although statistical results were not reported. Five-year estimates of disease-free survival (using biochemical failure definitions) did not statistically differ between groups. The other study involved comparisons of bowel- and urinary-related QoL in three distinct cohorts receiving PBT (n=95; 74-82 GyE), IMRT (n=153; 76-79 Gy), or 3D-CRT (n=123; 66-79 Gy). Statistical changes were assessed within (but not between) each cohort immediately following treatment as well as at 12 and 24 months of follow-up, and were also assessed for whether the change was considered "clinically meaningful" (>0.5 SD of baseline values). Some differences in QoL decrements were seen at earlier timepoints. However, at 24 months, all groups experienced statistically and clinically significant decrements in bowel QoL, and none of the groups had significant declines in urinary QoL.

A fourth, poor-quality comparison of case series involved an evaluation of patient-reported outcomes on the Expanded Prostate Cancer Index Composite (EPIC) questionnaire among a cohort of 1,243 patients receiving PBT for prostate cancer and a group of 204 patients receiving IMRT from a previous multicenter study. Statistically-significant differences between treatment groups were observed for many baseline characteristics, only some of which were adjusted for in multivariate analyses. No differences were observed in summary scores for bowel, urinary, and sexual QoL at two years, although more IMRT patients reported specific bowel frequency (10% vs. 4% for PBT, p=0.05) and urgency (15% vs. 7%, p=0.02) problems at two years.

Harms

Four comparative studies examined the harms associated with PBT and alternative treatments in patients with prostate cancer. The previously-described RCT of PBT+photon therapy vs. photons alone examined rates of rectal bleeding, urethral stricture, hematuria, incontinence, and loss of full potency; no patients in either arm had grade 3 or higher toxicity during radiation therapy. Actuarial estimates of rectal bleeding at eight years were significantly higher in the PBT+photon arm (32% vs. 12% for photons alone, p=0.002), although this was primarily grade 2 or lower toxicity. Rates of urethral stricture, hematuria, incontinence, and loss of potency did not differ between groups.

Three additional studies involved retrospective comparisons using available databases. The most recent was a matched comparison of 314 PBT and 628 IMRT patients treated for early-stage prostate cancer using the linked Chronic Condition Warehouse-Medicare database with a focus on complications occurring within 12 months of treatment. At six months, rates of genitourinary toxicity were significantly lower in the PBT arm (5.9% vs. 9.5%, p=0.03). This difference was not apparent after 12 months of follow-up, however (18.8% vs. 17.5%, p=0.66). Rates of gastrointestinal and other (e.g., infection, nerve damage) complications did not statistically differ at either timepoint.

Another recent study compared matched cohorts of men with prostate cancer in the linked Medicare-SEER database who were treated with PBT or IMRT (684 patients in each arm) and followed for a median of four years. IMRT patients had a statistically-significantly lower rate of gastrointestinal morbidity (12.2 vs. 17.8 per 100 person-years, $p<0.05$). No other statistical differences were noted in genitourinary morbidity, erectile dysfunction, hip fracture, or use of additional cancer therapy.

Finally, there was an analysis of nearly 30,000 men in the Medicare-SEER database who were treated with PBT, IMRT, 3D-CRT, brachytherapy, or conservative management (observation alone) and evaluated for gastrointestinal toxicity. All forms of radiation had higher rates of GI morbidity than conservative management. In pairwise comparisons using Cox proportional hazards regression, PBT was associated with higher rates of GI morbidity than conservative management (HR: 13.7; 95% CI: 9.1, 20.8), 3D-CRT (HR: 2.1; 95% CI: 1.5, 3.1), and IMRT (HR: 3.3; 95% CI: 2.1, 5.2).

In summary, moderate evidence suggests that rates of major harms are comparable between PBT and photon radiation treatments, particularly IMRT.

Noncancerous Conditions

Ocular Hemangiomas

Curative

A single poor-quality retrospective study evaluated PBT's clinical effectiveness in 44 patients with diffuse or circumscribed choroidal hemangiomas who were treated with either PBT (20-23 GyE) or photon therapy (16-20 Gy) and followed for an average of 2.5 years. Unadjusted outcomes were reported for the entire cohort only; reduction in tumor thickness, resolution of retinal detachment, and stabilization of visual acuity were observed in >90% of the overall sample. In Kaplan-Meier analysis of outcomes adjusting for differential follow-up between treatment groups, therapeutic modality had no statistically-significant effects on stabilization of visual acuity ($p=0.43$).

Harms

A single, previously-described retrospective comparative cohort study assessed outcomes in patients with circumscribed or diffuse hemangiomas treated with PBT or photon radiation. Small differences in unadjusted rates of optic nerve/disc atrophy, lacrimation (formation of tears) and ocular pressure as well as effects on the retina, lens, and iris were observed between groups, but most side effects were grade 1 or 2. The rate of retinopathy was substantially higher in PBT patients (40% vs. 16% for photons). However, in Cox proportional hazards regression adjusting for between-group differences, no effect of radiation modality on outcomes was observed, including retinopathy ($p=0.12$).

Other Benign Tumors

Curative

Two comparative studies of PBT's clinical effectiveness in other benign tumors were both of poor quality. One was a retrospective cohort of consisting of 20 patients with giant-cell bone tumors who were treated with PBT+photon therapy (mean: 59 GyE) or photons alone (mean: 52

Gy) and followed for median of 9 years. Patients could also have received partial tumor resection. Of note, the PBT population consisted entirely of young adults (mean age: 23 years), while the photon-only population was much older (mean: 46 years); no attempt was made to control for differences between treatment groups. Rates of disease progression, progression-free survival, and distant metastases were numerically similar between groups, although these rates were not statistically tested.

The other study was a small cohort study comparing PBT alone, photon therapy alone, or PBT + photons in 25 patients with optic nerve sheath meningioma. On an overall basis, visual acuity improved in most patients. Rates did not numerically differ between treatment groups, although these were not tested statistically.

Salvage

In the first study described above, five of 20 were identified as having recurrent disease. Two of the five were treated with PBT+photon therapy, one of whom had progression of disease at eight months but no further progression after retreatment at five years of follow-up. The other patient was free of local progression and metastases as of 9 years of follow-up. In the three photon patients, one had local progression at 12 months but no further progression as of year 19 of follow-up, one patient was free of progression and metastases as of five years of follow-up, and one patient had unknown status.

Harms

The previously-described study comparing PBT, PBT+photon, and photon therapy alone in 25 patients treated for optic nerve sheath meningiomas showed numerically lower rates of acute orbital pain and headache for both PBT groups compared to photon therapy, and numerically higher rates of late asymptomatic retinopathy. None of these comparisons were tested statistically, however. Evidence is limited and inadequate to compare the potential harms of PBT relative to other radiation modalities in patients with other benign tumors.

Cost & Cost-Effectiveness

Limited data are available about costs of PBT in most types of cancer. One study of breast cancer patients in the US examined reimbursement for treatment with 3D-conformal partial breast irradiation using protons or photons vs. traditional whole breast irradiation. Payments included those of treatment planning and delivery as well as patient time and transport. Total per-patient costs were substantially higher for PBT vs. photon partial irradiation ($13,200 vs. $5,300) but only modestly increased relative to traditional whole breast irradiation ($10,600), as the latter incurred higher professional service fees and involved a greater amount of patient time. Two additional studies from the same group assessed the cost-effectiveness of PBT vs. photon radiation among women with left-sided breast cancer in Sweden. In the first of these, photon radiation was assumed to increase the risk of ischemic and other cardiovascular disease as well as pneumonitis relative to PBT; clinical effectiveness was assumed to be identical. Reductions in adverse events led to a gain in quality-adjusted life years (QALYs) equivalent to approximately one month (12.35 vs. 12.25 for photon). Costs of PBT were nearly triple those of photon therapy, however ($11,124 vs. $4,950), leading to an incremental cost-effectiveness ratio (ICER) of $65,875 per QALY gained. The other study used essentially the same model but

focused attention only on women at high risk of cardiac disease (43% higher than general population). In this instance, a much lower ICER was observed ($33,913 per QALY gained).

One study evaluated the economic impact of PBT in lung cancers among patients in the Netherlands. A Markov model compared PBT to carbon-ion therapy, stereotactic radiation therapy, and conventional radiation in patients with stage 1 non-small-cell lung cancer (NSCLC) over a 5-year time horizon. Effects of therapy included both overall and disease-related mortality as well as adverse events such as pneumonitis and esophagitis. For inoperable NSCLC, PBT was found to be both more expensive and less effective than either carbon-ion or stereotactic radiation and was therefore not included in subsequent analyses focusing on inoperable disease. While not reported in the paper, PBT's derived cost-effectiveness relative to conventional radiation (based on approximately $5,000 in additional costs and 0.35 additional QALYs) was approximately $18,800 per QALY gained.

Three decision analyses were available that focused on pediatric cancers, all of which focused on a lifetime time horizon in children with medulloblastoma who were treated at 5 years of age. In a US-based model that incorporated costs and patient preference (utility) values of treatment and management of adverse events such as growth hormone deficiency, cardiovascular disease, hypothyroidism, and secondary malignancy, PBT was found to generate lower lifetime costs ($80,000 vs. $112,000 per patient for conventional radiation) and a greater number of QALYs (17.37 vs. 13.91). Reduced risks for PBT were estimated based on data from dosimetric and modeling studies. Sensitivity analyses on the risk of certain adverse events changed the magnitude of PBT's cost-effectiveness, but it remained less costly and more effective in all scenarios.

Pediatric medulloblastoma was assessed in two modeling studies. As with the analysis above, PBT was assumed to reduce both mortality and nonfatal adverse events relative to conventional photon therapy. On a per-patient basis, PBT was assumed to reduce lifetime costs by approximately $24,000 per patient and increase quality-adjusted life expectancy by nearly nine months (12.8 vs. 12.1 QALYs). On a population basis, 25 medulloblastoma patients treated by PBT would have lifetime costs reduced by $600,000 and generate an additional 17.1 QALYs relative to conventional photon radiation.

Finally, four studies were identified that examined costs and cost-effectiveness of PBT for prostate cancer. An analysis of the 2008-2009 Chronic Condition Warehouse examined treatment costs for matched Medicare beneficiaries with prostate cancer who received PBT or IMRT. Median Medicare reimbursements were $32,428 and $18,575 for PBT and IMRT respectively (not statistically tested).

A relatively recent Markov decision analysis estimated the lifetime costs and effectiveness of PBT, IMRT, and stereotactic body radiation therapy (SBRT) for localized prostate cancer. Clinical effectiveness and impact on mortality were assumed to be equivalent across all three groups. SBRT was found to have the lowest treatment costs and shortest time in treatment of the three modalities, and produced slightly more QALYs (8.11 vs. 8.05 and 8.06 for IMRT and PBT respectively) based on an expected rate of sexual dysfunction approximately half that of IMRT or PBT. SBRT was cost-saving or cost-effective vs. PBT in 94% of probabilistic simulations.

An earlier decision analysis estimated the potential cost-effectiveness of a hypothetically-escalated PBT dose (91.8 GyE) vs. 81 Gy delivered with IMRT over a 15-year time horizon. The model focused on mortality and disease progression alone (i.e., toxicities were assumed to be similar between groups), and assumed a 10% reduction in disease progression from PBT's higher dose. This translated into QALY increases of 0.42 and 0.46 years in 70- and 60-year-old men with intermediate-risk disease respectively. Costs of PBT were $25,000-$27,000 higher in these men. ICERs for PBT vs. IMRT were $63,578 and $55,726 per QALY for 70- and 60-year-old men respectively.

Finally, the model also evaluated costs and outcomes for a hypothetical cohort of 300 65 year-old men with prostate cancer. PBT was assumed to result in a 20% reduction in cancer recurrence relative to conventional radiation as well as lower rates of urinary and gastrointestinal toxicities. PBT was estimated to be approximately $8,000 more expensive than conventional radiation over a lifetime but result in a QALY gain of nearly 4 months (0.297). The resulting cost-effectiveness ratio was $26,481 per QALY gained.

EVIDENCE SUMMARY

Proton beam therapy (PBT) has been used for clinical purposes for over 50 years and has been delivered to tens of thousands of patients with a variety of cancers and noncancerous conditions. Despite this, evidence of PBT's comparative clinical effectiveness and comparative value is lacking for nearly all conditions under study in this review. As mentioned previously, it is unlikely that significant comparative study will be forthcoming for childhood cancers despite uncertainty over long-term outcomes, as the potential benefits of PBT over alternative forms of radiation appear to be generally accepted in the clinical and payer communities. In addition, patient recruitment for potential studies may be untenable in very rare conditions (e.g., thymoma, arteriovenous malformations). In other areas, however, including common cancers such as breast and prostate, the poor evidence base and residual uncertainty around the effects of PBT is highly problematic.

The net health benefit of PBT relative to alternative treatments is rated "Superior" (moderate-large net health benefit) in ocular tumors and "Incremental" (small net health benefit) in adult brain/spinal and pediatric cancers. The net health benefit is judged "Comparable" (equivalent net health benefit) in several other cancers, including liver, lung, and prostate cancer, as well as ocular hemangiomas. It should be noted, however, that judgments of comparability were made based on a limited evidence base that provides relatively low certainty that PBT is roughly equivalent to alternative therapies. While further study may reduce uncertainty and clarify differences between treatments, it is currently the case that PBT is far more expensive than its major alternatives, and evidence of its short or long-term relative cost-effectiveness is lacking for many of these conditions. It should also be noted that evidence was examined for 11 cancers and noncancerous conditions not listed above, and it was determined that there was insufficient evidence to obtain even a basic understanding of PBT's comparative clinical effectiveness and comparative value.

GRADE-Informed Framework

The HERC develops recommendations by using the concepts of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for carrying out the steps involved in developing recommendations. There are four elements that determine the strength of a recommendation, as listed in the table below. The HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Balance between desirable and undesirable effects, and quality of evidence, are derived from the evidence presented in this document, while estimated relative costs, values and preferences are assessments of the HERC members.

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
PBT for ocular tumors (excluding hemangiomas)	Superior benefit, fewer harms	Moderate	Moderate; expensive, but lowered projected costs due to greater benefit and fewer harms	Low variability (preference for PBT)	Recommended for coverage (*strong recommendation)*	Moderate quality evidence demonstrates PBT is superior to other therapies with fewer harms, although at a greater cost, and many patients would choose this.
PBT for adult malignant brain/spinal tumors	Comparable benefit but fewer harms.	Very Low**	Moderate; expensive, but lowered projected costs due to fewer harms	Low variability (preference for PBT)	Recommended for coverage (*weak recommendation*)	There is very low quality evidence of incremental benefit compared to alternatives, but also with higher costs. People would likely choose what is thought to have fewer harms and greater benefit.

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
PBT for skull base, paranasal sinus, and juxtaspinal tumors	Comparable benefit but fewer harms.	Very Low**	Moderate, expensive, but lowered projected costs due to fewer harms	Low (preference for PBT)	Recommended for coverage *(weak recommendation)*	The subcommittee heard expert testimony that skull-base tumors were one of the first uses of proton beam therapy in the 1960s and that reduction in harms to surrounding structures while delivering adequate dosimetry to tumor tissue is the primary consideration in treatment planning. Based on comparable benefit and fewer harms, allowing for higher costs but patient preference, weak recommendation for coverage.

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
PBT for malignant pediatric tumors	Comparable benefit but fewer harms.	Very Low**	Moderate, expensive, but lowered projected costs due to fewer harms	Moderate (significant concerns regarding radiation therapy, given variety of tumors may have options for alternative therapies)	Recommended for coverage *(weak recommendation)*	Very low quality evidence suggests comparable benefit, and fewer harms, with a potential health impact over decades. There is a strong theoretical benefit for reducing secondary tumors although there is not good evidence to support this. Cost-effectiveness analyses suggest long term cost savings with PBT for pediatric tumors. There is a lack of clinical equipoise and therefore future studies on this are unlikely.
PBT for liver cancer	Comparable benefit, comparable harms	Low	High	Moderate	Do not recommend (*weak recommendation*)	There is sufficient evidence that PBT has comparable benefits and harms to alternatives, but is more expensive,
PBT for lung cancer	Comparable benefit, comparable harms	Low	High	Moderate	Do not recommend (*weak recommendation*)	Sufficient evidence of similar effectiveness, similar risk, and more cost.

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
PBT for prostate cancer	Comparable benefit, comparable harms	Low	High	Moderate	Do not recommend (*weak recommendation*)	There is sufficient evidence of similar effectiveness, similar risk, and more cost. There may be improved local control in poorly differentiated prostate cancer (Glisan 4-5) but no demonstrated impact on survival.
PBT for ocular hemangiomas	Comparable benefit, comparable harms	Very Low	High	Moderate to high, due to uncertainty of benefit	Do not recommend *(weak recommendation)*	Insufficient evidence exists, but it is suggesting comparable benefit. Given that there are alternatives available with similar risk and less expensive, recommendation against coverage.

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
PBT for bone, breast, oropharyngeal, nasopharyngeal, esophageal, GI, gynecologic, lymphomas, sarcomas, seminomas, thymomas, AVMs, and other noncancerous conditions	Unknown	Bone: Low All others: No evidence	High	Moderate (many would not choose PBT due to cost, need to travel, uncertain benefit)	Do not recommend (weak recommendation)	Insufficient evidence, unknown risk compared to alternative, and increased cost.

*The Quality of Evidence rating was assigned by the primary evidence source, not the HERC Subcommittee, except as specified.

** The Quality of Evidence rating was assigned by the HERC Subcommittee.

Note: GRADE framework elements are described in Appendix A

POLICY LANDSCAPE

Quality measures

No quality measures were identified when searching the National Quality Measures Clearinghouse.

Professional society guidelines

Guidelines on the use of proton beam therapy are available from the National Comprehensive Cancer Network (NCCN, 2013-2014), American Society for Radiation Oncology (ASTRO, 2013), American College of Radiology (ACR, 2011-2013), American Cancer Society (ACS), and the Alberta Health Services in Canada (2013).

Bone Cancer

NCCN guidelines state that for unresectable high- and low-grade chondrosarcomas of the skull base and axial skeleton, PBT may be indicated to allow for high-dose treatment. Alberta guidelines recommend PBT for sarcomas, including chordoma and chondrosarcoma. According to the ACR, PBT-based treatment plans are considered inappropriate (rated 1-2) in spinal and non-spinal bone metastases.

Brain, Spinal, and Paraspinal Tumors

Alberta guidelines recommend PBT as an option for CNS lesions including craniopharyngioma, germ cell tumors and low-grade gliomas.

Head and Neck Cancers

For ethmoid and maxillary sinus tumors, NCCN considers PBT an investigative therapeutic technique only. Alberta guidelines state that treatment with PBT for adults with acoustic neuromas, and paranasal sinus and nasal cavity tumors is recommended.

Lung Cancer

NCCN considers PBT appropriate for non-small-cell lung cancer. ACR recommends against use of PBT for NSCLC patients with poor performance status or requirements for palliative treatment, while Alberta guidelines do not recommend PBT for NSCLC.

Lymphomas

NCCN states that PBT may be appropriate for patients with Hodgkin and Non-Hodgkin lymphoma as well as soft tissue sarcomas; however, long-term studies are necessary to confirm benefits and harms. Alberta guidelines do recommend PBT for lymphomas only in patients less than 30 years of age.

Ocular Tumors

NCCN guidelines for treatment options in ocular tumors are under development. Alberta guidelines recommend PBT for ocular melanoma.

Pediatric Tumors

Guidelines from Alberta recommend consideration of PBT for pediatric tumors including ependymomas, rhabdomyosarcoma, Ewing's sarcoma, pineal tumors, and patients requiring craniospinal irradiation.

Prostate Cancer

NCCN and Alberta guidelines do not recommend PBT for use in prostate cancer, as superior or equivalent effects have not been demonstrated in comparison to conventional external-beam therapy. In a position statement, ASTRO concluded that the evidence supporting the use of PBT in prostate cancer continues to develop and define its role among current alternate treatment modalities. ASTRO strongly supports the provision of coverage with evidence development to evaluate the comparative effectiveness of PBT relative to other options including IMRT and brachytherapy. The ACR Appropriateness Criteria® consider PBT for treatment planning in T1 and T2 prostate cancer to be appropriate but with lower ratings than for IMRT (6-7 versus 8-9, based on a 1-9 scale).

Non-cancerous conditions

Alberta Health Services guidelines recommend PBT for benign conditions such as AVMs and meningiomas.

Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

APPENDIX A. GRADE ELEMENT DESCRIPTIONS

Element	Description
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Resource allocation	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted

Strong recommendation

In Favor: The subcommittee is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.
Against: The subcommittee is confident that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Weak recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.
Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Quality or strength of evidence rating across studies for the treatment/outcome[1]

High: The subcommittee is very confident that the true effect lies close to that of the estimate of the effect. Typical sets of studies are RCTs with few or no limitations and the estimate of effect is likely stable.
Moderate: The subcommittee is moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.
Low**:** The subcommittee's confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

[1] Includes risk of bias, precision, directness, consistency and publication bias

***Very low*:** The subcommittee has very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

APPENDIX B. APPLICABLE CODES

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
170.0-170.9	Malignant neoplasm of bone and articular cartilage
171.0-171.9	Malignant neoplasm of connective and other soft tissue
189.0	Malignant neoplasm of kidney, except pelvis
190.0	Malignant neoplasm eyeball, except conjunctive, cornea, retina, choroids
190.5	Malignant neoplasm of retina
190.6	Malignant neoplasm of eye, choroid
191.0-191.9	Malignant neoplasm of brain
192.1-192.3	Malignant neoplasm of cerebral meninges, spinal cord, spinal meninges
194.0	Malignant neoplasm of adrenal gland
194.3	Malignant neoplasm of pituitary gland and craniopharyngeal duct
194.4	Malignant neoplasm of pineal gland
198.3	Secondary malignant neoplasm, brain and spinal cord
209.29	Malignant carcinoid tumors of other sites
225.0-225.9	Benign neoplasm of brain and other parts of nervous system
227.3	Benign neoplasm of pituitary gland
234.8	Carcinoma in situ of other specified sites (pituitary)
237.0	Neoplasm of uncertain behavior of pituitary gland
239.7	Neoplasm of unspecified nature, endocrine gland (pituitary)
437.3	Cerebral aneurysm, non-ruptured
437.8-437.9	Other and unspecified cerebrovascular disease
747.81	Anomalies of the cerebrovascular system (AVM)
185	Malignant neoplasm of prostate
198.82	Secondary malignant neoplasm, genital organs
233.4	Carcinoma in situ, prostate
ICD-10 Diagnosis Codes	
C40.00-C41.9	Malignant neoplasm of bone and articular cartilage
C47.0-C47.9	Malignant neoplasm of peripheral nerves and autonomic nerves
C49.0-C49.9	Malignant neoplasm of other connective and soft tissue
C64.1-C64.9	Malignant neoplasm of kidney, except renal pelvis
C69.20-C69.22	Malignant neoplasm of retina
C69.30-C69.32	Malignant neoplasm of choroid
C69.40-C69.42	Malignant neoplasm of ciliary body
C70.0-C70.9	Malignant neoplasm of meninges
C71.0-C71.9	Malignant neoplasm of brain
C72.0-C72.9	Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system
C74.00-C74.92	Malignant neoplasm of adrenal gland
C75.1-C75.3	Malignant neoplasm of pituitary gland, craniopharyngeal duct, pineal gland
C7A.8	Other malignant neuroendocrine tumors
C79.31	Secondary malignant neoplasm of brain
C79.40-C79.49	Secondary malignant neoplasm of other and unspecified parts of nervous system
D09.3	Carcinoma in situ of thyroid and other endocrine glands [pituitary]
D32.0-D32.9	Benign neoplasm of meninges

D33.0-D33.9	Benign neoplasm of brain and other parts of central nervous system
D35.2	Benign neoplasm of pituitary gland
D44.3-D44.4	Neoplasm of uncertain behavior of pituitary gland, craniopharyngeal duct
D49.7	Neoplasm of unspecified behavior of endocrine glands and other parts of nervous system [pituitary]
I67.1	Cerebral aneurysm, nonruptured
I67.89-I67.9	Other and unspecified cerebrovascular disease
Q28.2	Arteriovenous malformation of cerebral vessels
C61	Malignant neoplasm of prostate
C79.82	Secondary malignant neoplasm of genital organs
D07.5	Carcinoma in situ of prostate
ICD-10 Procedure Codes	
D0004ZZ	Beam radiation of brain using heavy particles (protons, ions)
D0014ZZ	Beam radiation of brain stem using heavy particles (protons, ions)
D0064ZZ	Beam radiation of spinal cord using heavy particles (protons, ions)
D0074ZZ	Beam radiation of peripheral nerve using heavy particles (protons, ions)
D8004ZZ	Beam radiation of eye using heavy particles (protons, ions)
DP004ZZ-DP0C4ZZ	Beam radiation of bone using heavy particles (protons, ions) [by site; includes codes DP004ZZ, DP024ZZ, DP034ZZ, DP044ZZ, DP054ZZ, DP064ZZ, DP074ZZ, DP084ZZ, DP094ZZ, DP0B4ZZ, DP0C4ZZ]
DT004ZZ	Beam radiation of kidney using heavy particles (protons, ions)
DW014ZZ	Beam radiation of head and neck using heavy particles (protons, ions)
DW024ZZ	Beam radiation of chest using heavy particles (protons, ions)
DW034ZZ	Beam radiation of abdomen using heavy particles (protons, ions)
DW064ZZ	Beam radiation of pelvic region using heavy particles (protons, ions)
CPT Codes	
32701	Thoracic target(s) delineation for stereotactic body radiation therapy (SRS/SBRT), (proton or particle beam), entire course of treatment
77373	Stereotactic body radiation therapy, treatment delivery, per fraction to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions
77421	Stereoscopic X-ray guidance for localized of target volume for the delivery of radiation therapy
77432	Stereotactic radiation treatment management of cranial lesion(s) (complete course of treatment consisting of 1 session)
77435	Stereotactic body radiation therapy, treatment management, per treatment course, 1 or more lesions, including image guidance, entire course not to exceed 5 fractions
77520	Proton treatment delivery; simple, without compensation
77522	Proton treatment delivery; simple, with compensation
77523	Proton treatment delivery; intermediate
77525	Proton treatment delivery; complex
HCPCS Level II Codes	
S8030	Scleral application of tantalum ring(s) for localization of lesions for proton beam therapy

Note: Inclusion on this list does not guarantee coverage

Proton Beam therapy Coverage Guidance and the Prioritized List

Question: Proton Beam therapy and the Prioritized List

Question source: HTAS, HERC Staff

Issue: The DRAFT Coverage Guidance on Proton Beam Therapy has been approved through HTAS. It needs to be applied to the Prioritized List.

Proton beam therapy (PBT) is recommended for coverage for malignant ocular tumors (*strong recommendation*).

Proton beam therapy is recommended for coverage *(weak recommendation)* for:

- malignant brain, spinal, skull base, paranasal sinus, and juxtaspinal tumors
- pediatric malignant tumors (incident cancer under age 21)

Proton beam therapy is not recommended for coverage for cancer of the bone, breast, oropharynx, nasopharynx, esophagus, liver, lung, or prostate or for gynecologic or gastrointestinal cancers, lymphoma, sarcoma, thymoma, seminoma, arteriovenous malformation or ocular hemangiomas *(weak recommendation).*

Current Prioritized List Status:

Code	Description	List Status
77520	Proton treatment delivery; simple, without compensation	117 CANCER OF EYE AND ORBIT 130 BENIGN NEOPLASM OF THE BRAIN AND SPINAL CORD 299 CANCER OF BRAIN AND NERVOUS SYSTEM 377 BENIGN NEOPLASM OF RESPIRATORY AND INTRATHORACIC ORGANS
77522	Proton treatment delivery; simple, with compensation	117,130,299,377
77523	Proton treatment delivery; intermediate	117,130,299,377
77525	Proton treatment delivery; complex	117,130,299,377

HERC Staff Assessment

Proton beam therapy codes are currently placed on four lines, only two of which are for malignant tumors. The other two lines (intrathoracic and brain) are for benign tumors only, which requires review. Because of the new proposed coverage of

pediatric malignant tumors, there will be multiple additional lines to which these codes would need to be added.

HERC Staff Recommendations:

1) **Add proton beam therapy codes to the following lines** (based on expert recommendation):
    a. 97 CHILDHOOD LEUKEMIAS
    b. 133 GRANULOMATOSIS WITH POLYANGIITIS
        i. This is because the lethal midline granuloma code (M31.2) is on this line
    c. 195 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER
    d. 205 CANCER OF BONES
    e. 242 ACUTE PROMYELOCYTIC LEUKEMIA
    f. 280 CANCER OF SKIN, EXCLUDING MALIGNANT MELANOMA
    g. 292 CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX
    h. 402 ACUTE MYELOID LEUKEMIA
    i. 403 MYELOID DISORDERS

2) **Consider removal of proton beam therapy codes** from:
    a. Line 130 BENIGN NEOPLASM OF THE BRAIN AND SPINAL CORD
    b. Line 377 BENIGN NEOPLASM OF RESPIRATORY AND INTRATHORACIC ORGANS

3) **Add a new guideline**
    GUIDELINE NOTE XXX PROTON BEAM THERAPY FOR CANCER
    Lines 97, 117, ~~130,~~ 133, 195, 205, 242, 280, 292, 299, ~~377,~~ 402, 403
    Proton beam therapy is included on these lines only for:
    - malignant ocular tumors
    - malignant brain, spinal, skull base, paranasal sinus (including lethal midline granuloma), and juxtaspinal tumors
    - pediatric malignant tumors (incident cancer under age 21) in, or adjacent to, critical structures

HERC Coverage Guidance – Proton Beam Therapy
Disposition of Public Comments

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Commenters

Identification	Stakeholder
A	Seattle Cancer Care Alliance Proton Therapy Center, Medical Director (Washington State)
B	Patient (Washington State)
C	Assistant professor, Department of Radiation Oncology, University of Washington, Seattle Cancer Care Alliance (Washington State)
D	Friend of patient
E	Friend of patient (Washington State)
F	Friend of patient (Washington State)
G	Radiation Oncologist, Corvallis, OR
H	Assistant Professor, Department of Radiation Oncology, University of Washington Medical Center (Washington State)
J	Professor and Chair, Dept. of Radiation Medicine/Professor, Division of Hematology/Oncology, Knight Cancer Institute, Oregon Health & Science University
K	Citizen (no further info provided) (Washington State)
L	Radiation Oncology, University of Washington
M	Health Policy Analyst, American Society for Radiation Oncology (ASTRO)
N	Assistant Professor, Department of Radiation Oncology, Department of Neurological Surgery, UW School of Medicine
O	Friend of patient
P	President, Particle Therapy Cooperative Group – North America
Q	Associate Professor, University of Washington Medical Center, Department of Radiation Oncology
R	Assistant Professor, University of Washington Department of Radiation Oncology
S	Associate Professor, University of Washington Department of Radiation Oncology
T	Retired nurse, Lynden, WA
U	Prostate cancer patient (WA)
V	Unknown

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W	Assistant Professor, University of Washington Department of Radiation Oncology
X	Unknown
Y	Executive Director, National Association for Proton Therapy

Public Comments

ID	#	Comment	Disposition
A	1	Thank you for the opportunity to submit scientific information on Proton Beam Radiation Therapy (PBRT). PBRT eliminates the exit radiation dose that patients would otherwise receive if treated with X-rays, thereby protecting normal tissue from damaging radiation exposure. This technique allows the oncologist to (1) increase the dose delivered to tumor in order to improve local control (LC) for radiation resistant tumors and/or (2) reduce acute and long-term morbidity by minimizing normal tissue exposure. These benefits translate into not only an improvement in clinical outcomes, but quality of life and reduction of the short and long-term cost of side effect management due to functional impairment. For these reasons, we feel that it is important that Oregon residents continue to have access to this important weapon for the treatment of cancer. We welcome the opportunity to serve as an on-going resource to this Commission.	Thank you for your comments.
A	2	National Coverage Guidance Supporting the Use of Proton Beam Therapy The National Comprehensive Cancer Network (NCCN) guidelines support the use of protons for a variety of malignancies where clinical outcomes with standard therapy is suboptimal.	NCCN guidelines are summarized in the document under "Policy Landscape."
A	3	Additionally, a number of distinguished national cancer organizations have released model policy guidelines for the judicious and appropriate coverage for PBRT in patients who are most likely to benefit.	Specific guidelines are not named by the commenter. The CG document lists guidelines from the National Comprehensive Cancer Network (NCCN, 2013-2014), American Society for Radiation Oncology (ASTRO, 2013), American College of Radiology (ACR, 2011-2013), American Cancer Society (ACS), and the Alberta Health Services in Canada (2013).
A	4	We also note that the Medicare contractor for Oregon currently provides for PBRT coverage.	Thank you for the information.
A	5	The model policy from the American Society for Radiation Oncology (ASTRO), the pre-eminent and largest radiation oncology organization, released after the Washington HTA report, is one that we call your attention as strong initial	ASTRO guidelines are considered under the "Policy Landscape"

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ID	#	Comment	Disposition
		policy framework for coverage.	section of the CG document; a model payer policy is not appropriate for inclusion as evidence.
A	6	2014 Washington State Health Care Authority Health Technology Assessment (HTA) The 2014 Washington HTA on PBRT highlighted the need to gather additional clinical data. We agree with this; in fact, 97% of patients treated at our center are enrolled in either a clinical trial or prospective registry. While long-term efficacy and toxicity data is maturing, we routinely utilize dosimetric comparative data to determine appropriate utilization of PBT. For this reason, we feel that excluding all comparative dosimetric studies was a significant methodological flaw in the Washington HTA report. Dosimetric data is routinely utilized for clinical decision making in radiation oncology. In short, if you can deliver greater dose to the tumor or reduce normal tissue exposure, this is expected to benefit our patients. Finally, we strongly encourage you to support payer coverage with clinical evidence generation for disease sites where dosimetric comparisons suggest superiority of PBT, but clinical evidence is not yet available.	Dosimetric comparative trials of proton beam therapy would only be applicable to this coverage guidance if conventional modalities (such as IMRT) were one of the treatment arms, or if comparison to conventional radiotherapy were not feasible to obtain.
A	7	Summary of Evidence The body of clinical evidence supporting the appropriate use of protons continues to grow. Due to space considerations, we present a small sampling of the evidence. However, we remain available to present a more comprehensive view to this Commission	Thank you for presenting additional sources of evidence.
A	8	*Head & Neck Cancers* – A comparative effectiveness study from MD Anderson suggests that use of intensity modulated PBRT in advanced stage head and neck cancer was less costly and of higher value than IMRT [Frank et al, Oncology Payers 2014] (1).	Frank et al is a costing analysis comparing the experiences of two individual patients. Oncology Payers is not a peer-reviewed journal and is not identified by MEDLINE®, it does not meet the standard for inclusion.
A	9	A meta-analysis evaluating the role of photons and charged particle therapy for sinonasal carcinoma demonstrated improved disease-free survival (DFS) and LC with charged particle therapy; subgroup analysis comparing IMRT and PBRT confirmed that 5-year DFS was significantly higher at five years for patients receiving PBRT (72% versus 50%) [Patel et al, Lancet Oncol 2014] (2).	Patel 2014 was published after the WAHTA, which judged evidence to be insufficient on head & neck cancers. It is a MA of 43 cohorts. A subgroup analysis comparing proton beam

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			therapy with intensity-modulated radiation therapy showed significantly higher disease-free survival at 5 years (relative risk 1·44, 95% CI 1·01–2·05; p=0·045) and locoregional control at longest follow-up (1·26, 1·05–1·51; p=0·011). Authors encourage prospective study with patient-oriented outcomes to confirm findings. This level of evidence is generally not considered sufficient to guide coverage; however, the subcommittee discussed that RCTs may not be feasible or ethical in this setting and that reduced harms in treatment of sinonasal carcinoma with PBT would justify a recommendation for coverage.
A	10	*Breast Cancer*– A recent population-based study of 2168 woman, [Darby et al N Engl J Med. 2013] (3) found that collateral radiation exposure to the heart during breast cancer X-ray treatment increases the subsequent rate of ischemic heart disease.	Darby et al conducted a case-control study of major coronary events in patients who underwent radiotherapy for breast cancer from 1958 to 2001 in Sweden and Denmark. This was prior to modern advances in radiotherapy when radiation doses are generally lower, and does not address comparative safety of PBT.

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A	11	PBRT can significantly reduce this exposure. Macdonald et al reported the results of a prospective trial of protons after mastectomy for patients with excellent clinical outcome and significant reduction in heart dose when compared to X-rays. [Macdonald et al Int J Radiat Oncol Biol Phys. 2013] (4)	MacDonald et al is a noncomparative study of 12 individuals receiving PBT for breast cancer. While a lower heart dose theoretically will decrease future toxicity, study authors concluded "it is too early to determine cardiopulmonary toxicities in our study" as follow-up was conducted at 4 and 8 weeks.
A	12	*Prostate Cancer*– In a recent publication from the University of Florida, 5 year outcomes from 3 prospective trials of PBT for prostate cancer were reported. Five year rates of biochemical and clinical freedom from disease progression were 99%, 99%, and 76% in low, intermediate, and high risk patients, respectively. Reported toxicity rates were low. These results compare very favorably with those published for IMRT. [Mendenhall et al, Int J Radiat Oncol Biol Phys 2014] (5). We highlight our center's participation in the ongoing "PartiQOL" randomized trial comparing IMRT vs protons for prostate cancer.	The Mendenhall study is a noncomparative observational study of 211 patients; its early outcomes (2012) are included in Table 13, Appendix F (single-arm case series) of the WA HTA report.
A	13	*The True Cost of Protons*- In addition to the significant and growing body of clinical evidence, the cost-effectiveness of PBRT has also been explored. We would highlight that although PBRT is more resource-intensive to deliver upfront, it is aligned with the judicious use of health care dollars. Several recent studies, including these from Harvard have shown that when the costs of side-effects are accounted for, PBRT actually significantly *reduces* health care costs when compared to standard radiation therapy. Therefore, protons when used appropriately are *cost-effective* when compared to photon beam radiotherapy due to reduced hospitalization rates, etc. for side effect management. [Mailhot-Vega Cancer 2013 (6); Mailhot-Vega Cancer 2015 (7)].	Mailhot-Vega 2013 is included in the Washington HTA analysis. Mailhot-Vega 2015 is a Markov cohort-simulation model looking specifically at growth-hormone deficiency in pediatric cancers.
A	14	We urge the Commission to support the coverage of proton therapy and welcome the opportunity to serve as an on-going resource as you are assessing this promising cancer therapy option for Oregonians.	Thank you for your comments.
B	15	I am commenting on the proposed policy regarding Proton Therapy.	Thank you for your comments.
B	16	I was diagnosed in February 2012 with prostate cancer after having a biopsy. My PSA reading had been climbing the previous 2 years and when it reached 10.7, I had the biopsy done. The biopsy showed that I had cancer. My urologist, who was a surgeon, suggested having surgery in August of 2012. He also set me up to speak to a radiation oncologist. I had a CT & Pet scan plus explanations on the different forms of radiation treatments that were available, conventional x-	Thank you for your comments. The coverage guidance does reference one fair-quality prospective cohort study of

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ID	#	Comment	Disposition
		rays and seeds. Also at this time I joined a local prostate support group. I spoke with the men in the support group plus other men I had met that had prostate cancer to find out how they were doing. I spoke with the men who had surgery or either of the two forms of radiation treatments done. Many of them had procedures done years before. None had Proton Therapy or had heard of it. Every single man I spoke with, no matter how healthy they were or how well their procedure went were still having some form of issue. The two main areas of problems were incontinence and sexual function. They had different degrees of problems, from slight to serious, but all of them had something.	patient-reported quality of life among 185 men treated for prostate cancer. "No differences in overall QoL or general health status were observed at 18 months of follow-up" (p 13).
B	17	I spoke with a former vice president of my company who was treated for prostate cancer 6 years before at Loma Linda with Proton Therapy. He has had no long-term side effects. When he did his research he talk to over 100 Proton Therapy patients and came to the conclusion that because of the minimal long term side effects it was the best way to go. So I started researching on the Internet and found the same information about the lack of side effects with Proton Therapy. Also, at that time I found out that a Proton Therapy facility was being built in Seattle and would open spring of 2013. I made my decision that this was the best way to go. I went for 9 weeks of treatment; I continued to work the whole time not missing a single day. I went to work in the morning, went for treatments during midday, and then returned to work after treatment. I had no issues during treatment. By the way, I am a bicycle commuter (year round), I ride round trip 14 miles a day for work and I continued to do this even during my treatments. My wife would pick me up and take me to treatments. I am also an avid cross-country skier during the winter months.	Thank you for your comments.
B	18	My urologist had told me that if I had done surgery I would be off work for about 3 months, if I had selected x-rays or seeds I would be off work also for a period of time. Since the end of my treatments I have had 6 follow up PSA tests and my reading keeps going down. It is 0.52 now from the high of 10.7. I have had absolutely no side effects from the Proton treatment since completing treatment in June 2013. I continue to ride my bike to and from work each day. Each August I do a bike ride of 186 miles, which I do with my son each year. No problems. I don't believe I would be doing any of this or enjoying it as much if I had incontinence issues. Try biking or skiing wearing some form of diaper. Can it be done, yes. Would it be enjoyable, probably not. There has been no change in my health from before Proton treatment to now, except the lack of cancer. Is Proton Therapy the right treatment for everyone? I can't answer that, only a doctor or a person with prostate cancer can answer that. But in my case I thank God I found out about it and decided to go that route for treatment.	Thank you for your comments.
B	19	One thing I keep noticing about this whole debate about insurance companies not wanting to pay for Proton Therapy is it seems to come down to cost. Yes, proton Therapy is more expensive than the other more "accepted" forms of cancer treatment, but does anyone actually look at the long term cost from the possible long-term side effects of surgery, x-rays or seeds? I have never seen it mentioned anywhere. Quite frankly it seems no one really cares about the cost of side effects once the patient is out the door. But to me having to spend the rest of my life possibly in diapers or on some other form of medicine for side effects did not thrill me at all. By the way I am 61 years old. I plan on being around for quite a while longer.	Cost and cost-effectiveness analyses, including costs of adverse effects, are considered in the CG document.

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ID	#	Comment	Disposition
B	20	The last thing I want to say is, please don't take away or limit the Proton Therapy option for others who may come after me.	Thank you for your comments.
C	21	After reviewing the commission's draft on coverage guidance for proton beam therapy (PBT), I would like to highlight and summarize the pertinent, existing evidence supporting the selective use of protons as part of lymphoma treatment.	Thank you for your comments.
C	22	Lymphoma is a heterogeneous disease entity comprised of Hodgkin (HL) and non-Hodgkin lymphoma (NHL). As such, the decision on which radiation technique is best suited for a patient (e.g. PBT vs IMRT/VMAT vs 3D vs other) incorporates multiple variables including patient age, tumor location, and histology.	Thank you for your comments.
C	23	The commission is correct that currently no clinical outcomes data exists comparing photons and protons among HL or NHL patients. In HL patients, in whom the goal is to minimize morbidity and toxicity without compromising already excellent cure rates, the outcomes of interest (e.g. cardiovascular disease [CVD], second malignancy [SM]) generally require at least a decade of follow-up as no intermediate biomarker currently exists as a short-term endpoint.	Thank you for your comments. It is noted that improvements in long-term toxicities will take time to appear in trials.
C	24	Up to 75% of HL patients have disease in the thorax, and the long-term radiation-associated morbidity to this area has been clearly documented including increased rates of cardiac events (1), decreased lung function (2), breast cancer (3), lung cancer (4) and esophageal cancer (5). Furthermore, in these studies, the risk of a SM increased with increasing radiation dose to the lung, breast, or esophagus (i.e. linear no threshold), implying that the lower the radiation dose to these structures, the lower the risk of SM.	Thank you for providing these data on the risk of secondary malignancy in treatment of Hodgkins lymphoma.
C	25	Risk of toxicity appears related to the radiation dose to and volume of normal thoracic structure irradiated (2, 6) and likely will decline in the future as radiation dose and target volumes (i.e. involved-node versus involved field radiation) are currently being reduced. Nonetheless, radiation technique (PBT vs other) may still play an important role as dosimetric comparative studies using modern radiation target volumes and dose demonstrate that, on average, PBT was associated with lower dose to the heart, lungs, and breasts compared with 3D conformal and VMAT photon techniques (7). Based on risk estimates, proton technique was associated with the lowest life-years lost (7). Other dosimetric comparison studies have also shown similar, significant reduction of dose to the heart (8), breast (9, 10), lung (9, 10), and total body (9).	Commenter provides background information on risk of damage to surrounding structures with conventional radiation, and posits that PBT provides lower dose to such structures.
C	26	Thus far, the early results of involved-node radiation with protons demonstrate excellent relapse-free and event-free survival (11), suggesting that target volume coverage and local control is not compromised by using a more conformal technique. Admittedly, the ten to twenty year-local control, event-free survival, overall survival, and late toxicity after treatment with involved-node proton radiation, as compared with 3D conformal photon radiation, will be the gold standard on which to base clinical decisions and cost-effective analyses. Cost can be calculated over various time periods, but arguably for lymphoma patients, this time period should be evaluated over at least 20-30 years, which is	Commenter notes that Hodgkins patients can expect to live decades, making late toxicity an important outcome. However, late toxicity would also be a concern for other cancers that

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ID	#	Comment	Disposition
		when late effects of treatment may manifest and impact the patient, medical system, and society from a productivity and financial standpoint. By reducing dose to normal organ structures without compromising oncologic outcomes, protons may, in the long term, be associated with less cost secondary to fewer complication rates. Until then, I would urge you to consider the existing, preliminary data suggesting the dosimetric advantages of protons for treatment of lymphoma. Rapid adoption of reduced target volumes (e.g. involved-node radiation) among the radiation oncology community has, in part, been driven by the basic understanding that reducing dose to surrounding normal tissues will decrease acute and late morbidity for our patients.	occur in early adulthood with a high likelihood of survival. Recommendation for noncoverage was made due to lack of comparative clinical outcomes data. In cases where clinical outcomes data could be obtained, dosimetric information was felt to be inadequate to demonstrate a superior clinical outcome.
C	27	Please do not hesitate to contact me if you have any additional questions, clarifications, or concerns.	Thank you for your comments.
D	28	I support and encourage your covering proton radiation therapy for all forms of cancer or at least liver cancer where it has proven to be efficacious. I encourage you to begin covering it now, not in 3, 5, 10 years. A very close friend of our's sister needs this therapy immediately. She needs your help. She is 'covered' by Regence Blue Shield OR. After all, is that not what insurance is for. Thank you	Commenter addresses Regence; nevertheless, thank you for your comments.
E	29	Please set the example for the country. We have these therapies that give people hope to live longer, yet we make it such a fight. Not fair to family and sick person. I am not sure why drug company does not pay for some of this with regency insurance or any insurance. Please help families stop suffering and let insurance companies and drug companies work together for these treatments. Advocating for our sick health system to get better and for my friend who wants to try this treatment.	Commenter is a resident of Washington State. Thank you for your comments.
F	30	Please cover proton therapy for all forms of cancer, or at very least, liver cancer. Our close friend's sister from Medford is dying of liver cancer, has been approved for proton therapy, but pending insurance coverage decision by Oregon. Thank you for your consideration of this live saving request.	Commenter is a resident of Washington State. Thank you for your comments.
G	31	Between 1984 and 1988 I was a faculty member in the department of Radiation Oncology at Massachusetts General Hospital and Harvard Medical School. My primary clinical responsibility was proton radiation treatment at the Harvard Cyclotron Laboratory which was the first proton facility in the US. Subsequently I spent 18 years in the Department of Radiation Oncology at the University of Washington School of Medicine. Since 2006 I have been in a community practice in Corvallis. Oregon.	Thank you for your comments.
G	32	Through my years in practice I have used virtually all types of radiation treatments available for treating malignancies.	Thank you for your comments.

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ID	#	Comment	Disposition
		Protons have the very significant advantage of delivering the lowest integral dose to a patient; in other words, normal tissues receive less dose with protons than with any other type of radiation including intensity modulated photon radiation treatments. Randomized control studies and nonrandomized comparative studies as discussed in the HERC document show at least equivalent tumor control rates for PBT compared to photons in many tumor types with decreased toxicity in some tumor sites.	Studies mentioned by commenter are addressed in CG document.
G	33	Decreased integral dose with PBT has considerable advantages in pediatric malignancies. Growth and development are adversely impacted by radiation. PBT causes less injury. The HERC document describes several studies demonstrating the benefits of PBT in pediatric patients. Secondary malignancy reduction takes many years of followup to study. Preliminary data as cited in this document indicates a reduction in secondary malignancy.	As noted on Table 1, PBT was judged to have incremental net health benefit for pediatric cancers.
G	34	Primary brain, skull base and spinal malignancies also benefit from PBT because of decreased integral dose. The physical/spatial characteristics of PBT allow sufficient dose to be delivered to skull base and primary spinal malignancies. All parts of the brain perform important functions. PBT reduces dose to uninvolved areas of the brain in primary brain tumor treatment. This benefit in neurological function can be difficult to demonstrate using standard methods, but with sufficiently sensitive measurements improved function would mostly likely be seen.	As noted on Table 1, PBT was judged to have incremental net health benefit for adult brain/spinal tumors.
G	35	I strongly suggest that HERC reconsider their coverage recommendations to align with the Washington State HTCC recommendations.	Thank you for your comments.
H	36	Thank you for the opportunity to submit scientific information on Proton Beam Radiation Therapy (PBRT). PBRT eliminates the exit radiation dose that patients would otherwise receive if treated with X-rays, thereby protecting normal tissue from damaging radiation exposure. This technique allows the oncologist to (1) increase the dose delivered to tumor in order to improve local control (LC) for radiation resistant tumors and/or (2) reduce acute and long-term morbidity by minimizing normal tissue exposure. These benefits translate into not only an improvement in clinical outcomes, but also quality of life and reduction of the short and long-term cost associated with side effect management. For these reasons, we feel that it is important that Oregon residents continue to have access to this important weapon for cancer treatment.	See comment A1.
H	37	PBRT for non-small cell lung cancer (NSCLC) is currently recommended by the National Comprehensive Cancer Center Guidelines (NCCN V4.2014) and should not be considered experimental, investigational, or unproven.	Guidance from professional organizations on PBRT for lung cancer is mixed. NCCN does recommend; however ACR and Alberta guidelines do not. The SR finds comparable benefits and harms at increased cost; therefore the recommendation

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ID	#	Comment	Disposition
			is to not cover.
H	38	*Locally Advanced NSCLC*: Definitive chemoradiotherapy is the standard of care for locally advanced non-small cell lung cancer, however this treatment has the potential to carry significant toxicity. At present, LC with standard dose radiotherapy in locally advanced disease is suboptimal, with 50-60% patient experiencing relapse of their disease. One approach to improve LC is increasing the radiation dose delivered to the cancer. However, this potential improvement comes at the expense of greater toxicity. Unfortunately, attempts at dose escalation with standard X-rays in lung cancer have hit a 'toxicity ceiling' whereby the resulting increased toxicity from dose actually may reduce survival, based upon a recent randomized trial with X-rays (1).	Commenter references Bradley JD et al 2015, demonstrating that 74Gy radiotherapy had no additional benefit and possibly increased mortality compared to 60Gy radiotherapy, or a "toxicity ceiling."
H	39	In a phase II trial of dose-escalated PBRT concurrent with chemotherapy for 44 patients with stage III NSCLC, MD Anderson demonstrated reduced the side effects, which permitted safe dose escalation to 74 Gy (2). The median overall survival time was 29.4 months, compared with 19 months for patients who were treated with 74Gy with X-rays in RTOG 0617. No patient experienced grade 4 or 5 proton-related adverse events. Based upon these promising results, the RTOG has launched a phase III randomized trial of protons vs photons (RTOG 1308) for locally advanced NSCLC. Our center is participating in this trial.	Commenter notes ongoing research on PBRT in locally-advanced NSCLC given evidence of superior tumor control when 74 Gy is delivered via PBT (Chang 2011, case series of 44 patients). A Phase III trial is in progress. Three comparative studies discussed in the CG have found that "rates of treatment-related toxicities with PBT are comparable to those seen with other radiation modalities in patients with lung cancer."
H	40	*Medically Inoperable Early Stage NSCLC:* The current standard therapeutic approach for these patients is stereotactic body radiation therapy (SBRT) or hypofractionated radiotherapy with photons, which provide excellent results. However, patients with centrally located tumors are at a11-fold higher risk of high-grade toxicity or death with SBRT due to radiation exposure to the heart and mediastinal structures. (3) Therefore until a "safe dose" is established, SBRT with photons is relatively contraindicated in patients with centrally located tumors.	Commenter references Timmermann 2006, study of SBRT in 70 patients too frail to undergo surgical resection of NSCLC. Hilar/pericentral location was a strong predictor of high-grade toxicity. No comparison to PBRT is included.
H	41	Bush *et al*. reported the long-term results of a prospective trial of high-dose hypofractionated PBRT for 111 patients with medically inoperable NSCLC. OS improved with increasing dose (51, 60, and 70 Gy) with a 4-year OS of 18%, 32%,	Commenter notes that SBRT may not be used for centrally located tumors, whereas PBRT

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		and 51%, respectively (P=0.006). (4)	may improve survival by allowing delivery of higher radiation doses. The studies of PBRT in medically inoperable NSCLC were non-comparative and were included in the review by the Washington HTA. Additionally, there is an ongoing RCT (NCT00915005) comparing photon and proton therapy for locoregionally advanced NSCLC (stages II-IIIb, no specific exclusion of patients with medically inoperable tumors).
H	42	Additionally, patients with centrally located tumors did not experience excessive or increased toxicity when compared with peripherally located tumors. (4) This is in contrast to the clinical experience with X-rays. These prospective studies demonstrate that protons are safe and effective for patients with centrally located NSCLC who are medically inoperable. This has ***not*** yet been demonstrated with X-rays.	See comment H41.
H	43	*Patients with NSCLC who require re-irradiation:* Options are limited for patients previously treated with radiation and who subsequently experience intrathoracic NSCLC recurrence. These patients have a poor response to chemotherapy; surgery is extremely high-risk and usually contraindicated.	Commenter notes patients who fail initial radiation have limited options.
H	44	Due to their favorable dose-deposition characteristics, protons are uniquely suited to delivery radiation in this clinical setting. The MD Anderson group reported the results on thirty-one patients (94%) who completed reirradiation with protons. At a median 11 months' follow-up, 1-year rates of overall survival, progression-free survival, locoregional control, and distant metastasis-free survival were 47%, 28%, 54%, and 39%. Rates of severe (grade 3) toxicity were 9% esophageal, 21% pulmonary; 1 patient had grade 4 esophagitis, and 2 had grade 4 pulmonary toxicity. These data demonstrate the feasibility and efficacy of PBRT in this clinical setting. (5)	There is no comparative evidence currently available that demonstrates the superiority of PBRT to other forms of radiation therapy, surgery, chemotherapy, or palliative care for intrathoracic recurrence of NSCLC.
H	45	*The Cost of Protons for Lung Cancer*- Patients with lung cancer experience significant toxicity with standard X-ray based therapy.	Commenter references evidence of toxicity above, see H 40.
H	46	Emerging data demonstrate that protons, when used appropriately, can be *cost-effective* when compared to photon	See comment A 13.

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		beam radiotherapy due to reduced hospitalization rates, etc. for side effect management. (6,7)	
H	47	We performed a similar analysis of cost using these methods for lung cancer patients and found that for patients treated with IMRT experiencing high grade pulmonary or esophageal toxicities had costs that ***exceeded*** patients treated with protons without this toxicity.	Commenter notes internal analysis demonstrating cost savings with decreased toxicity. Reference to publication not provided.
H	48	We urge the Commission to support the coverage of proton therapy for lung cancer and welcome the opportunity to serve as an on-going resource as you are assessing this promising cancer therapy option for Oregonians. Thank you for this opportunity.	Thank you for your comments.
J	54	Thank you for the opportunity to submit scientific information on Proton Beam Radiation Therapy (PBRT). I am writing this letter to you in my capacity as Chairman of the Department of Radiation Medicine at Oregon Health Sciences University (OHSU). At the present time, OHSU does not have a proton beam facility and we do not derive any financial benefit from the delivery of proton beam radiation to patients in Oregon. However, we feel that it is important that Oregon residents have access to this important weapon for the treatment of cancer and have sent a number of our patients to proton beam facilities in other states. We send these select patients for proton radiation because we feel strongly that it is in their best clinical interest. While we do not feel that all patients benefit from protons, there are patients, especially pediatric patients in whom protons allow us to reduce risk of normal tissue injury due to radiation exposure in a manner that simply is not achievable with X-rays.	Thank you for your comments.
J	55	National Coverage Guidance Supporting the Use of Proton Beam Therapy I would like to highlight that a number of distinguished national cancer organizations have released model policy guidelines for the judicious and appropriate coverage for PBRT in patients who are most likely to benefit. I would call to your attention that the current draft of the HERC guidelines are out of step with these guidelines.	Guidelines from several organizations are included in the CG document under the "Policy Landscape" section and were considered by the HTAS.
J	56	The model policy from the American Society for Radiation Oncology (ASTRO), the pre-eminent and largest radiation oncology organization, released after the Washington HTA report, is one that we call your attention as a strong initial policy framework for coverage.	See comment A 5.
J	57	I would strongly encourage you to support payer coverage with clinical evidence generation for disease sites where dosimetric comparisons suggest superiority of PBT, but clinical evidence is not yet available. The value of this approach is highlighted in the article by Bekelman and Hahn in the Journal of Clinical Oncology (Bekelman and Hahn, JCO 2014).	Commenter suggests recommendation for coverage with evidence development. Discussion of coverage with evidence development and/or reference pricing is not in the

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			purview of this subcommittee.
J	58	Summary of Evidence The body of clinical evidence supporting the appropriate use of protons continues to grow. Due to space considerations, I am presenting a small sampling of the evidence.	Thank you for your comments.
J	59	Pediatric Tumors: In a landmark article, Oeffinger et al [N Engl J Med, 2006] showed that pediatric patients had between 5-10 times the risk of developing severe health complications after radiotherapy compared to their untreated siblings. For medulloblastomas where the radiation treatment involves the brain and spinal cord, data from MD Anderson shows that the ratio of relative risk (RRR) (proton/photon) of cardiac mortality ranged from 0.12 to 0.24. Obviously this is a substantial reduction in risk of injury and mortality in pediatric patients receiving proton beam radiotherapy [Zhang, Rad & One, 2014]	Oeffinger 2006 refers to the Childhood Cancer Survivor Study, a retrospective study of 10,397 survivors and 3034 siblings, which assessed incidence of chronic health conditions among cancer survivors compared to cancer-free siblings. Zhang 2014 is a treatment planning study of 17 pediatric medulloblastoma patients. "Passively scattered proton CSI provides superior predicted outcomes by conferring lower predicted risks of second cancer and cardiac mortality than field-in-field photon CSI for all medulloblastoma patients in a large clinically representative sample in the United States, but the magnitude of superiority depends strongly on the patients' anatomical development status." HTAS has chosen to recommend coverage of PBT for pediatric patients.
J	60	In the case of rhabdomyosarcomas of the head and neck, particularly the orbit, proton radiotherapy allows the	Childs 2012 is included in the

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		treatment of the tumor with much less dose to the brain and growing bones of the skull. Childs et al [Int J Radiat Oneal Bioi Phys, 2012] reported on 17 patients with parameningeal tumors treated at the Massachusetts General Hospital and found local control rates similar to historical treatments with photon radiotherapy but with fewer side effects. Similar considerations apply when treating neuroblastomas and Wilms tumors where standard photon treatments give higher radiation doses to the bowel and kidneys than would be delivered with protons.	WAHTA report.
J	61	Brain tumors as a class are the most common pediatric solid tumor. Merchant et al reviewed neurocognitive data for patients treated at St. Jude's, correlated this with radiation doses delivered to various areas of normal brain, calculated the doses that would have been delivered with proton radiotherapy and concluded that the reduced dose afforded by proton radiotherapy resulted in significantly less IQ deterioration than standard radiotherapy [Merchant et al, Pediatr Blood Cancer, 2008].	The referenced study collected radiation dose data for 40 patients, estimated dose that would have been received with PBRT, and applied a model of cognitive impact. The model suggests PBRT may have a lower cognitive impact for pediatric brain tumors. Comparative trials on this outcome are unlikely due to lack of clinical equipoise. The subcommittee recommended coverage of PBT for pediatric tumors.
J	62	Head & Neck Cancers -A meta-analysis evaluating the role of photons and charged particle therapy for sinonasal carcinoma demonstrated improved disease-free survival (DFS) and LC with charged particle therapy; subgroup analysis comparing IMRT and PBRT confirmed that 5-year DFS was significantly higher at five years for patients receiving PBRT (72% versus 50%) [Patel et al, Lancet Oncol 2014].	See also comment A9 regarding Patel 2014. PBT for sinonasal carcinoma is recommended for coverage.
J	63	Breast Cancer-A recent population-based study of 2168 woman, [Darby et al N Engl J Med. 2013] found that collateral radiation exposure to the heart during breast cancer X-ray treatment increases the subsequent rate of ischemic heart disease. PBRT can significantly reduce this exposure. Macdonald et al reported the results of a prospective trial of protons after mastectomy for patients with excellent clinical outcome and significant reduction in heart dose when compared to X-rays. [Macdonald et al Int J Radiat Oneal Bioi Phys. 2013]	See comments A10, A11.
J	64	The Cost of Protons for Children-The cost-effectiveness of PBRT in pediatric malignancies has been explored. We would highlight that although PBRT is more resource-intensive to deliver upfront, it is aligned with the judicious use of health care dollars. Lundqvist et al examined the cost of proton beam radiotherapy for childhood medulloblastoma and found that proton therapy was associated with €23,600 in cost savings and 0.68 additional quality-adjusted life-years per	Lundkvist 2005 is discussed extensively in the WAHTA report used for this CG.

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		patient. The analyses showed that reductions in IQ loss and GHD contributed to the greatest part of the cost savings and were the most important parameters for cost-effectiveness. [Lundqvist et al, Cancer 2005]	
J	65	We urge the Commission to support the coverage of proton therapy for a broader range of cancers and specifically highlight pediatric tumors and welcome the opportunity to serve as an on-going resource as you are assessing this promising cancer therapy option for Oregonians. Thank you for taking time to review this letter.	Thank you for your comments.
K	66	Dear Regence, I am writing to encourage you to examine your policy of not covering Proton Therapy where it has been proven effective, such as in the treatment of liver cancer. I think that all insurers should now be offering coverage for this approach to treating disorders in which it has been shown to be efficacious.	Commenter addresses Regence; nevertheless, thank you for your comments.
L	67	We are faculty members of the Department of Radiation Oncology at the University of Washington. The majority of our head and neck patients are not treated with protons; we use it selectively in cases where we feel there is a benefit over standard forms of radiotherapy. While the Seattle Cancer Care Alliance Proton Center is one of the sites where our group practices, we have no equity interest in the center. There is no financial incentive for us to treat patients there as opposed to other sites. We would like to call your attention to the following literature:	Thank you for your comments. WAHTA included two very small poor-quality comparative cohort studies for head & neck cancer. References submitted by this commenter are all non-comparative. It may be that individual tumor types are rare enough and proximal tissues sensitive enough that comparative studies are not feasible. Following public comment and expert testimony, the subcommittee recommended coverage of PBT for certain head and neck cancers; namely, skull-base tumors, paranasal sinus tumors, and juxtaspinal tumors.
L	68	Skull Base Tumors One of the challenges with skull-based tumors is their proximity to the brainstem and optic structures, which can be dose-limiting organs when treating relatively radio resistant histologies such as chordomas and chondrosarcomas. With conventional photon radiotherapy, dose is limited to 55 Gy and associated with an inferior local control (LC) rate of	Commenter notes poor local control rate when dosimetry is limited by nearby organs. Reference 1 is a review article from 1999. Direct comparative

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<tr><td></td><td></td><td>approximately 30-50% (1). In contrast, LC for these skull-based chordomas and chondrosarcomas is higher with charged particle therapy, as summarized in the following table:</td><td>studies are not provided. HTAS recommends skull base tumors for coverage.</td></tr>
<tr><td>L</td><td>69</td><td>TABLE: LC Rates for Sarcomas or Chordomas of the Skull Base treated with α-Particles or Protons
<table>
<tr><th>Facility</th><th>Chordoma</th><th>Chondrosarcoma</th><th>Sarcoma (other)</th></tr>
<tr><td>LBNL (2)</td><td>63%</td><td>78%</td><td>58%</td></tr>
<tr><td>HCL-MGH (1,3)</td><td>59%</td><td>99%</td><td></td></tr>
<tr><td>LLUMC (3)</td><td>76%</td><td>92%</td><td></td></tr>
<tr><td>Orsay (4)</td><td>83%</td><td>90%</td><td></td></tr>
<tr><td>Tsukuba (5)</td><td>46%</td><td></td><td></td></tr>
<tr><td>PSI (6)</td><td>88%</td><td>100%</td><td></td></tr>
</table></td><td>Reference 2 is a 1994 case series of 223 patients treated from 1977-1992.

Reference 3 is a 1995 case series of 204 patients treated from 1975-1993.

Reference 4 is a 2001 case series of 45 patients treated from 1995-1998.

Reference 5 is a 2004 case series of 13 patients treated from 1989-2000.

Reference 6 is a 2005 case series of 29 patients treated from 1998-2003.

No comparative data are identified.

The subcommittee heard testimony that comparative data in this setting are not feasible. Treatment decisions are made by dosimetry calculations and these can be impacted by exposure of nearby structures. PBT for skull base tumors is recommended for coverage.</td></tr>
<tr><td>L</td><td>70</td><td>In the Loma Linda University Medical Center (LLUMC) series, all "small and medium size" tumors without brainstem involvement were controlled with only a 7% incidence of late toxicity. (3)</td><td>This case series of 204 patients was conducted from 1975-1993</td></tr>
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			and may not represent contemporary practice and technology.
L	71	Nasopharyngeal Carcinomas Compared with conventional radiotherapy, use of protons for treatment of nasopharyngeal carcinomas is associated with less dose to the optic structures, brain, and inner ears.	Thank you for your comments.
L	72	Lin et al reported on 16 patients with recurrent nasopharyngeal cancer who underwent proton reirradiation to 59.4-70.2 CGE after failing initial photon radiotherapy treatment to 50.0-88.2 Gy (7). Progression-free survival (PFS) was 50% at two years. Among those patients with "optimal" coverage, 2-year PFS was 83%. No patient had significant CNS toxicity.	Reference 7 is a 1999 case series of 16 patients. No comparative data are identified.
L	73	Chan et al reviewed outcomes for 17 patients with newly-diagnosed T4N0-3 nasopharyngeal tumors treated at either HCL-MGH or the Francis H. Burr Proton Therapy Center with combined proton and photon radiotherapy (8). The median prescribed dose was 73.6 CGE. Ten patients received induction and/or concomitant chemotherapy. LC and overall survival at 3 years were 92% and 74%, respectively.	Reference 8 is a 2004 case series of 17 patients treated from 1990-2002. No comparative data are identified.
L	74	Dosimetric comparative studies have demonstrated improved tumor coverage and conformality with intensity modulated proton therapy (IMPT) as compared to IMRT techniques. Given superior conformality, "avoidance structures" such as the spinal cord, inner ear, and middle ear received a 2-3 times lower median dose than with IMPT (9).	Reference 9 is a treatment planning study comparing potential radiation doses in 8 patients using IMRT or PBT. Study looked at planned/hypothetical radiation doses only.
L	75	Paranasal Sinus Tumors The close proximity of paranasal sinus tumors to brain and optic structures make these tumors amenable for proton radiotherapy. Among 14 patients with esthesioneuroblastomas treated with protons at Chiba, Japan, between 1999 and 2005, 5-year actuarial LC was 84% and overall survival was 93% (10).	Reference 10 is a retrospective cohort study of 14 patients treated from 1999-2005 in Japan. No comparative data are identified.
L	76	Chan et al reported on 91 patients with advanced paranasal sinus tumors who received combined photon and proton radiotherapy at the HCL-MGH to a mean dose of 73.6 CGE (11). The 3-year LC was 83% for squamous cell tumors, 91% for carcinomas having neuroendocrine features, 86% for adenoid cystic carcinomas, and 88% for sarcomas.	Reference 11 is a case series of 91 patients treated from 1988-2002. No comparative data are identified.
L	77	Lastly, outcomes among 1186 patients with paranasal sinus tumors treated with photons were compared with 286 patients treated with charged particle therapy in a meta-analysis. Overall survival and disease-free survival at 5 years	See also comment A9 regarding

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		were significantly higher among the charged particle therapy group. Among patients treated with proton radiotherapy versus IMRT, 5-year disease free survival and loco regional control at longest follow-up were higher among the proton radiotherapy group (12).	Patel 2014. PBT for sinonasal carcinoma is recommended for coverage.
L	78	Juxtaspinal Tumors When tumors are invasive or adherent to critical structures such as the vertebral body, spinal cord, or peripheral nerve roots, complete resection is difficult to achieve. Because the tumor is adjacent to the cord, with conventional radiotherapy techniques, dose to the tumor is limited by the cord's tolerance to radiation, 50-55 Gy. The use of protons or other charged particles allows one to wrap the high dose volume around and avoid the spinal cord; tumors can therefore be treated to 70 CGE with proton radiotherapy.	It is noted that radiation of juxtaspinal tumors is limited by tolerance of adjacent spinal cord.
L	79	Among 51 patients with cervical spine chordomas treated at MGH-HCL, LC was 65% (3). Nowakowski et al described a series of 52 patients with juxtaspinal tumors of varying histologies and locations treated with D-particles at the Lawrence Berkeley Laboratory; 16 of these were located in the cervical spine (13). The overall LC was 58% for 36 patients with previously untreated lesions.	Reference 3 is discussed under comment 69. Reference 13 is a case series of 52 patients treated from 1976-1987. No comparative data are identified.
L	80	Oropharyngeal Tumors Using a combination protons and photons in an accelerated fractionation schema, LLUMC treated 29 patients with locally-advanced, oropharyngeal carcinomas (13). The overall, 5-year actuarial loco regional control rate was 84% (88% primary site, 96% neck nodes); 5-year disease-free survival was 65%.	See comment 79.
L	81	Frank et al presented data at the 55th Annual Meeting of the American Society for Radiation Oncology showing that patients with orophalyngeal tumors treated with protons had a substantially lower requirement for feeding tubes during therapy than a comparable group of patients treated with IMRT (20% vs. 48%) and less nausea, emesis, and mucositis. A subsequent report on 15 head and neck cancer patients treated using multifield optimization of IMPT showed only one case of grade 3 mucositis in the posterior oral cavity; there was no grade 2 or higher mucositis in the anterior oral cavity (15).	Reference 15 is a case series of 15 patients, reporting "the first clinical experience and toxicity of multifield optimization (MFO) intensity modulated proton therapy (IMPT) for patients with head and neck tumors." No comparative data are identified.
L	82	Retreatment of Treatment Failures Management of patients with recurrent head and neck cancer who have failed an initial, radiation based treatment is challenging. Re-irradiation with photons, with or without chemotherapy, is associated with 34-65% grade 3+ toxicity. For	Reference 16 is a 2013 dose-planning study of 7 patients, comparing helical tomotherapy

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		non-nasopharyngeal sites, these serious side effects can include osteoradionecrosis, laryngeal and swallowing dysfunction and carotid artery ruptures (16). IMPT is significantly better than IMRT in terms of normal tissue sparing, particularly in the low to intermediate dose regions (17).	to IMPT. "IMPT was found not to be uniformly superior to HT… comparative dose planning is recommended if both methods are available." The subcommittee heard testimony that comparative dose planning is standard of care and that PBT will be recommended only when comparative dose planning finds it likely to be superior for a given patient. Coverage of PBT is recommended for malignant brain, spinal, skull base, paranasal, and juxtaspinal tumors [whether they are initial or recurrent]
M	83	Dear Commission Members: The American Society for Radiation Oncology* (ASTRO), appreciates the opportunity to comment on the Oregon Health Evidence Review Commission (HERC) Coverage Guidance for Proton Beam Therapy. We are concerned that the HERC Coverage Guidance is overly restrictive, inconsistent with current literature, and will have a detrimental effect on vulnerable populations who derive the most benefit from access to proton beam therapy.	Thank you for your comments.
M	84	Proton beam therapy (PBT) is neither a new nor an experimental technology for treating cancer with radiation. It utilizes proton radiation particles to deliver highly conformal radiation therapy to a specific tumor target area while giving a much lower dose to the normal tissues in the proton beam's path of entry and exit. PBT's reduced radiation dose to healthy tissues can reduce side effects for patients with demonstrated effectiveness in increasing quality of life. To date, scientific evidence exists confirming that PBT is particularly useful in a number of pediatric cancers, particularly those in the brain, as well as for certain adult cancers, such as ocular melanoma, chordoma, chondrosarcoma, and primary hepatocellular carcinoma. Patients with genetic syndromes and those with tumors near the spinal cord with previous irradiation also benefit from the use of PBT. Additional research on other cancer disease sites, such as breast, prostate and lung, is ongoing with NCI-supported clinical trials currently accruing patients in all three disease sites at the more than 14 proton therapy treatment centers around the country.	This information is correct and consistent with the CG report.

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M	85	In June 2014, ASTRO released a PBT Model Policy that identifies cancer diagnoses that meet ASTRO's evidence-based standards that should be covered by private insurers and Medicare. This Model Policy recommends two coverage groups for PBT: 1) patients with specific diagnoses for which PBT has been proven to be effective; and 2) patients with cancer diagnoses where there is a need for continued clinical evidence development and comparative effectiveness analyses for the appropriate use of PBT. For the patients in group two, coverage with evidence development is recommended for patients if they are enrolled in clinical trials or a multi-institutional registry to collect data and inform consensus on the role of proton therapy.	Please see comment 5.
M	86	The HERC Coverage Guidance is especially concerning because it declines to provide coverage for pediatric malignant tumors. PBT is an important treatment option for certain pediatric tumors, since damage to the surrounding normal tissues in children can produce serious long-term side effects on the growth and development of vital organs and tissues. A growing body of literature shows the late effects, quality of life, and cost effectiveness of proton beam therapy on pediatric patients. Randomized studies are not feasible given the general acceptance of PBT for pediatric patients within the expert community. To account for this, research compares these patients to appropriate historical cohorts. These studies are relatively "small" due to low incidence of these diseases; however, data are being collected prospectively for all children in single and multi-institutional databases. (1)	It is noted that comparative studies are unlikely to be conducted in pediatric tumors due to lack of clinical equipoise. The subcommittee recommended coverage of PBT for pediatric tumors.
M	87	Additionally, we are unaware of any coverage policies that deny coverage of PBT for pediatric tumors, and we are concerned that the denial of PBT coverage for pediatric patients will considerably restrict children's access to curative and palliative treatment. ASTRO strongly recommends that HERC extend coverage to include primary or benign solid tumors in children, per the ASTRO PBT Model Policy.	Thank you for your comments.
M	88	PBT has attracted significant attention due to its relative cost, which is usually higher than traditional external beam radiation therapy. However, studies now suggest that proton therapy can be a cost-effective strategy for the management of certain cancers. (2, 3, 4) In one study, proton beam therapy was proven to be associated with higher quality-adjusted life years and lower costs. (5)	The cost studies referenced were considered in the WAHTA report on which our CG is based.
M	89	Furthermore, we are concerned that in developing this coverage guidance, HERC did not consult the opinions of experts in the field nor did they review the full body of evidence surrounding proton beam therapy as an effective form of cancer treatment. We are very surprised that the ASTRO PBT Model Policy, which was carefully developed by leading radiation oncologists and medical physicists and benefitted from balanced input from experts in proton therapy, was not cited as a reference in the HERC Coverage Policy for Proton Beam Therapy.	The coverage guidance process solicits expert input as well as public comment such as this one. Please see comment 5 regarding ASTRO.
M	90	ASTRO is committed to providing evidence-based guidance to payers in the form of recommendations for correct coverage policies for radiation oncology. We encourage HERC to follow the lead of many national private and public insurers by consulting the evidence and following the recommendations in ASTRO's PBT Model Policy when developing coverage policies for PBT. The ASTRO PBT Model Policy is enclosed for your review, in addition to a list of references and	Thank you for your comments.

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		supporting articles.	
M	91	Thank you for your consideration of our comments. Should you have any questions or wish to discuss our concerns further, please contact ASTRO's Director of Health Policy	Thank you for your comments.
N	92	Dear Oregon Health Evidence Review Commission: As a Radiation Oncology faculty member at the University of Washington, I specialize in caring for patients of all ages with central nervous system tumors. A minority of my patients are treated with proton beam therapy. For these patients, proton beam therapy provides the best chance of curing their brain tumors while minimizing significant side effects. Proton beam therapy has no exit radiation dose, which patients would otherwise receive if treated with x-rays. This is especially important in the central nervous system where very low doses of radiation to normal brain can cause neurocognitive decline, hormonal deficits, and secondary malignancies. For spinal cases, low dose radiation to the anterior organs is associated with nausea and lower blood counts in the short term; and heart disease and secondary malignancies in the long term.	Thank you for your comments.
N	93	The Washington Health Technology Assessment recently issued a final report where they universally recommended that proton beam therapy for brain/spinal cancers be covered by state insurance. This was based on finding equal benefit and decreased harm for proton beam therapy over conventional therapy. In addition, many other coverage policies agree with this recommendation, and I urge you to do the same.	The WAHTA evidence report formed the basis for this CG document. Following the evidence report and public comment, the Health Technology Clinical Committee voted unanimously to recommend coverage of PBT with conditions, namely: - Ocular tumors - Pediatric cancers (e.g., medulloblastoma, retinoblastoma, Ewing's sarcoma) - Central nervous system tumors (e.g. brain, spinal and paraspinal tumors) - Other non-metastatic cancers with the following conditions: a) Patient has had prior

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			radiation in the expected treatment field with contraindication to all other forms of therapy, and b) At agency discretion Following public testimony and expert input, the subcommittee recommended coverage of PBT for malignant brain and spinal tumors.
N	94	Summary of Evidence *Pediatric central nervous system cancers:* Children have developing tissues that are exquisitely sensitive to radiation. Though long term survival is now achieved in the majority of patients, side effects from radiation therapy can have a profound effect on quality of life in survivors.	Please see comments 59 and 61.
N	95	In a study of patients receiving irradiation for a brain tumor before than age of four, only a third of adult survivors were able to have full-time employment. (1) Modeling of the effect of radiation therapy on IQ predicted a significant decrease in neurocognitive decline for older children as well. (2)	Reference 1 is a case series of 222 children treated from 1958-1995. Reference 2 is addressed in comment 61.
N	96	In a St Jude study of children treated for brain tumors, 94% had resulting growth hormone deficiency, 50% had hypothyroidism, and 43% had adrenal insufficiency.3 Proton therapy can decrease the pituitary dose for many cases.2	Please see comment 61.
N	97	Protons allow for sparing of the cochlea, resulting in lower ototoxicity rates. (4)	Reference 4 is considered in the WAHTA evidence review.
N	98	Finally, a recent study of pediatric patients with retinoblastoma showed that the 10 year cumulative incidence of secondary malignancy was 14% in patients treated with photons versus 0% in patients treated with protons. This supports the conclusion that protons will decrease the risk of secondary malignancy, which is 20.5% in 5 year survivors of childhood cancer. (5)	Reference for the comparative study of retinoblastoma treatment is not provided. Reference 5 is a case series of 14,359 survivors of childhood cancers; the 20.5% figure is correct.
N	99	*Adult low grade gliomas:* Recent multicenter randomized trials have shown median survival for patients with grade II	Reference 6 is a phase III trial

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		gliomas (both astrocytoma and oligodendroglioma) and grade III oligodendroglioma to now be greater than fourteen years with radiation therapy and chemotherapy. (6, 7) However, adult low grade glioma survivors have poor cognitive function when receiving postoperative radiation therapy, which limits their ability to work and decreases their quality of life. (8) A recent prospective phase II trial of proton beam therapy for low grade gliomas showed no evidence of overall decline in cognitive function or quality of life based on neurocognitive assessment and patient questionnaires. (9)	comparing chemotherapy + radiotherapy vs radiotherapy alone in 291 patients. Median survival was not different between groups for the whole cohort. The 14-year figure applies to patients with codeleted tumors only, which was not a predefined subgroup analysis. Reference 7 is an editorial describing long-term follow up results of the same study. Reference 8 is a cross-sectional study comparing self-reported cognitive function in 195 low-grade glioma survivors with 100 low-grade hematological patients and 195 healthy controls. The authors conclude that "Our findings suggest that the tumour itself has the most deleterious effect on cognitive function and that radiotherapy mainly results in additional long-term cognitive disability when high fraction doses are used." Reference 9 is a prospective single-arm cohort study of 20 patients followed for 5 years after proton therapy. No overall decline in cognitive function was detected.

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			Direct comparative data of PBT vs other treatment is not identified.
N	100	*Adult benign brain tumors (e.g. meningioma, vestibular schwannoma, pituitary adenoma):* Multiple series document the outcomes of proton therapy for the treatment of meningioma (10-13), pituitary adenoma (14), and vestibular schwannoma (15). For patients with benign disease and good long term prognosis, proton beam therapy decreases the risk of neurocognitive decline, endocrine dysfunction, and secondary malignancy. (16, 17)	References 10-13 are considered in the WAHTA evidence review. Reference 14 was published after the WAHTA review. It is a case series of 165 patients with functional pituitary adenoma treated from 1992-2012. Reference 15 is a case series of 64 patients treated with stereotactic radiation therapy. It did not discuss proton beam. No comparative data are identified. Reference 16 is a treatment-planning study of 10 patients in which treatment was re-planned with proton radiotherapy and effect differences were estimated based on hypothetical dose. Reference 17 is a similar modeling study in which doses are estimated using 8 different techniques in one standard case.
N	101	*Adult medulloblastoma:* The NCCN guidelines recommend considering proton therapy for craniospinal irradiation for adult medulloblastoma given published data by MD Anderson showing less weight loss and hematologic toxicity for patients undergoing proton therapy compared to photon therapy. (18)	Reference 18 is considered in the WAHTA review.
N	102	*High grade gliomas:* The median survival for glioblastoma multiforme is still roughly one year with chemotherapy and	It is noted that studies of proton

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		radiation therapy. Recent data suggests that increasing the radiation dose for initial treatment or giving a second course of radiation therapy for recurrent gliomas will improve outcomes. However, past efforts to escalate dose or re-irradiate have resulted in considerable toxicity. Thus, we are participating in two national cooperative group NRG Oncology clinical trials, BN001 and RTOG 1205. (19, 20) Both trials use proton therapy with the aim of improving survival for this otherwise devastating disease.	beam for GBM are in progress. Studies in progress will be considered after peer review and publication.
N	103	*Cost effectiveness:* Recent studies that modeled the cost of long term effects of radiation therapy for pediatric patients with brain tumors found that proton therapy is overall cost effective. (21, 22) Indeed, in my practice I find that long term survivors of brain tumors may be cured but have considerable late effects including neurocognitive decline and hormonal deficiency that are costly to the patient in terms of their ability to work and to payers in terms of medical care.	References 21 and 22 are the two papers by Mailhot Vega; please see comment 13.
N	104	I urge the Commission to support coverage of proton therapy for central nervous system tumors and welcome the opportunity to serve as an on-going resource as you are assessing this important cancer therapy option for Oregonians. Thank you for this opportunity.	Thank you for your comments.
O	105	To: Regence It has come to my attention that your insurance does not currently cover proton radiation treatment for all forms of cancer. I am writing to advocate that you at least provide your beneficiaries who have liver cancer, with this coverage. I hope you know that it has proven to be efficacious. Thank you for being responsive to the needs of your beneficiaries.	Commenter addresses Regence; nevertheless, thank you for your comments.
P	106	Dear Oregon Health Evidence Review Commission: On behalf of the Particle Therapy Cooperative Group- Nmih America (PTCOG-NA)1, we respectfully submit comments on Oregon's Health Evidence Review Commission (HERC) Coverage Guidance on Proton Beam Therapy (PBT).	Thank you for your comments.
P	107	While we were pleased to see the strong recommendation for coverage of malignant ocular tumors, we have significant concerns with many of the other recommendations. We were especially surprised and disappointed with the lack of a positive coverage recommendation for pediatric malignant tumors. Because of the strong evidence supporting its use, PBT for pediatric patients is practically universally covered. Additionally, we strongly disagree with your characterization that "PBT is far more expensive than its major alternatives." Recent studies have found that when treating for toxicity and other post-treatment occurrences are considered, PBT has been found to be a cost-effective treatment. We urge you to consider the evidence we provide in this letter in your deliberations.	Available cost-effectiveness data have been considered. The HTAS recommended coverage of PBT for pediatric tumors.
P	108	Evidence on the Effectiveness of PBT for Pediatric Malignant Tumors The proposed coverage guidance gave a weak recommendation for coverage for pediatric malignant tumors, despite the	The HTAS recommended coverage of PBT for pediatric

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		overwhelming consensus on its appropriateness for pediatric patients. We believe eliminating coverage of PBT for pediatric patients is inconsistent with the current state of evidence and would be harmful to a population of patients who would most benefit from the reduced amount of radiation received in the course of PBT treatment.	tumors.
P	109	Due to the growing body of evidence in this area, most payors, regulators and providers support the use of PBT for pediatric patients. The consensus is reflected in the American Society for Radiation Oncology (ASTRO) model policy on PBT which supports its use for primary or benign solid tumors treated in children with curative intent (ASTRO, 2014). (1) Examples of published evidence in this area include a recent study of 54 patients with pediatric rhabdomyosarcoma which found that PBT lowers integral dose and improves sparing normal tissue when compared to IMRT [Ladra, MM et al Radiother Oncol 2014]. (2)	Please see comment 5 regarding ASTRO. Ladra 2014 is a prospective cohort study of 54 patients who received proton therapy; IMRT plans were generated for comparison.
P	110	In another example, a 2012 study of high risk pediatric neuroblastoma found that preliminary outcomes reveal excellent control with proton therapy for this population [Hattagangadi JA, Int J Radiat Oncol Biol Phys, 2012]. (3) While we have cited just two studies, these are consistent with other studies of pediatric patients.	Hattangadi 2012 was considered in the WAHTA document.
P	111	Evidence on the Effectiveness of PBT for Other Sites The proposed guidance concludes, " ... there was insufficient evidence to obtain even a basic understanding of PBT's comparative clinical effectiveness and comparative value." Frankly, we were stunned by this characterization. While we acknowledge (and support) the ongoing development of additional clinical evidence, there is already significant evidence supporting the effectiveness of PBT that this proposed coverage guidance ignores. In addition to the evidence supporting the use of PBT for pediatric tumors, there is significant evidence supporting its use for other tumor sites.	The CG was based on a WAHTA report that came to this conclusion.
P	112	The articles listed below are only from the last 15 months and they reflect the meaningful research being conducted in this area. 2015 • Cuaron JJ, Chon B, Tsai H, Goenka A, DeBlois D, Ho A, Simon P, HugE, Cahlon 0 . Early toxicity in patients treated with postoperative proton therapy for locally advanced breast cancer. *Radiation Oncology.* Published online March 6, 2015. • Holliday EB, Mitra HS, Somerson JS, Rhines LD, Mahajan A, Brown PD, Grosshans DR. Postoperative proton therapy for chordomas and chondrosarcomas of the spine: adjuvant vs. salvage radiation therapy. *Spine.* Published online January 23, 2015. • Mizumoto M, Oshiro Y, Takizawa D, Fukushima T, Fukushima H, Yamamoto T, Muroi A, Okumura T, Koji T, Sakura H. Proton beam therapy for pediatric patients with ependymoma. *Pediatrics International.* 2015;	Cuaron (2015) is a case series that assessed dosimetry and early toxicity of PBT in 30 patients with metastatic breast cancer. Dosimetry was deemed adequate and toxicity was deemed acceptable. Holliday (2015) is a case series that assessed local control (58%), relapse-free survival (51.9%), and overall survival (93.3%) in 19 patients with

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		DOI:10.1111/ped.12624. • Vega RM, Kim J, Hollander A, Hattangadi-Giuth J, Michalski J, Tarbell NJ, Yock Tl, Bussiere M, MacDonald SM. Cost effectiveness of proton versus photon radiation therapy with respect to the risk of growth hormone deficiency in children. *Cancer.* Published online January 29, 2015. 2014 • Brower *N,* Gans S, Hartsell WF, Goldman S, Fangusaro JR, Patel N, Lulla RR, Smiley NP, Change JH, Gondi V. Proton therapy and helical tomothrapy result in reduced dose deposition to the pancreas in the setting of cranio-spinal irradiation for medulloblastoma: implications for reduced risk of diabetes mellitus in long-term survivors. *Acta Oncol.* 2014 Nov: 1-5. • Frank SJ, Cox JD, Gillin M, Mohan R, Garden AS, Rosenthal DI, Gunn GB, Weber RS, Kies MS, Lewin JS, Munsell MF, Palmer MB, Sahoo N, Zhang X, Liu W, Zhu XR. Multifield optimization intensity modulated proton therapy for head and neck tumors: a translation to practice. *Int J Radiat Oncol Bioi Phys.* 2014 Jul 15;89(4):846-53. • Kesarwala AH, Ko CJ, Ning H, et al. Intensity-modulated proton therapy for elective nodal irradiation and involved-field radiation in the definitive treatment of locally advanced non-small cell lung cancer: a dosimetric study. *Clinical Lung Cancer.* Available online 9 December 2014. • Ladra MM, Szymonifka JD, Mahajan A, et al. Preliminary results of a phase II trial of proton radiotherapy for pediatric rhabdomyosarcoma. *J Clin Oncol.* 2014 Oct 20; epub ahead of print. • Ling TC, Slater JM, et al. Analysis of intensity-modulated radiation therapy (IMRT), proton and 3D conformal radiotherapy (3D-CRT) for reducing perioperative cardiopulmonary complications in esophageal cancer patients. *Cancers.* 2014;6(4):2356-2368. • Makita C, Nakamura T, Takada A, Takayama K. Suzuki M, Amazi Y, Kato T, Tsukiyama I, Hareyama M, Kikuchi Y, Daimon T, Hata M, Inoue T, Fuwa N. High-dose proton beam therapy for stage I non-small cell lung cancer: clinical outcomes and prognostic factors. *Acta Oncol.* 2014Oct 7:1-8 (Epub ahead of print). • Patel SH, Wang Z, Wong WW, Murad MH, Buckey CR, Mohammed K, Alahdab F, Altayar 0, Nabhan M, Schild SE, Foote RL. Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: a systematic review and meta-analysis. *Lance/ Oncol.*2014 Aug; 15(9): I 028-1038. • Schild SE, Rule WG, Ashman JB, Vora SA, Keole S, Anand A, Liu W, Bues M. Proton beam therapy for locally advanced lung cancer: a review. *World J Clin Oncol.* 2014 Oct 10;5(4):568-75. • Sethi RV, Shih HA, Yeap BY, et al. Second nonocular tumors among survivors of retinoblastoma treated with	chordoma or chondrosarcoma treated with PBT. Patients with primary adjuvant radiation therapy had better 2 year LC than those receiving salvage treatment. Mizumoto (2015) is a case series that assessed local occurrence and toxicity in 6 pediatric patients with ependymoma treated with PBT. Simulation showed that PBT reduces dose to normal brain tissue by half compared to photon therapy. All patients were alive at follow up (13-44 mo) and there was no severe toxicity. Mailhot Vega (2015) is a cost-effectiveness study of PBT compared with photon therapy for pediatric patients with growth hormone deficiency.PBT is cost effective in some scenarios based on hypothalamic sparing. Brower (2014) is a case series that assessed dosimetry of PBT compared with 3DCRT and inverse-planned intensity modulated radiation therapy (IMRT) with helical tomotherapy in five pediatric patients with medulloblastoma. PBT resulted in less radiation to the pancreas

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		contemporary photon and proton radiotherapy. *Cancer.* 2014;120(1):126-133. • Thaker NG, Guzman AB, Feeley TW, Jones TM, lncalcaterra JR, Kolom C, Tatum LS, Walters RS, Cantor SB, Rosenthal DI, Garden AS, Gunn GB, Fuller CD, Palmer MB, Frank SJ. Defining the value of proton therapy using time-driven activity based costing. On col Payers 1 (1):22-28,2014. • Yock Tl, Bhat S, Szymonifka J, Yeap BY, Delahaye J, Donaldson SS, MacDonald SM, Pulsifer MB, Hill KS, DeLaney TF, Ebb D, Huang M, Tarbell NJ, Fisher PG, Kuhlthau KA. Quality of life outcomes in proton and photon treated pediatric brain tumor survivors. *Radiother Oncol.*2014 Oct 7. [Epub ahead of print]	than other treatments. Franks (2014) is a case series that assessed toxicity of multifield optimization intensity modulated PBT in 15 patients with head and neck cancer. There were no treatment-related deaths, and with a median follow-up time of 28 months (range, 20-35 months), the overall clinical complete response rate was 93.3% Kesarwala (2015) is a case series that assessed intensity-modulated PBT dosimetry in 20 patients with locally advanced non-small cell lung cancer. All evaluated dosimetric parameters improved significantly with proton plans compared with photon IFRT. Ladra (2014) is a case series that assessed disease control and toxicity of 57 pediatric patients with rhabdomyosarcoma treated with PBT. Five-year LC, EFS, and OS rates were similar to those observed in comparable trials that used photon radiation. Acute and late toxicity rates were favorable. Ling (2014) is a case series that assessed dosimetry of IMRT,

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			3DCRT and PBT in 10 patients with esophageal cancer. Authors conclude proton plans are technically feasible while achieving adequate coverage with lower doses delivered to the lungs and cardiac structures. Makita (2015) is a case series that assessed survival, local control, and toxicity in 56 patients with stage I non-small cell lung cancer treated with two PBT protocols. The three-year overall survival, progression-free survival, and local control rates were 81.3%, 73.4%, and 96.0%, respectively. There were no significant differences in outcomes between the two protocols. Late grade 2 and 3 pulmonary toxicities were observed in nine patients and one patient respectively; no grade 4 or 5 toxicities were observed. Patel (2014) is a systematic review and meta-analysis that compares clinical outcomes from PBT and charged particle therapy. Forty-one case series studies were included that reported on overall survival, disease-free survival, and local control. None of the included

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			studies were comparative. The review found higher overall survival and locoregional control for charged particle beam than PBT at longest follow-up (not defined), and no difference in disease-free survival at longest follow-up between groups. Schild (2014) is a narrative review on the use of PBT as part of a multi-modal treatment program for patients with locally advanced lung cancer. "This review was written for the non-radiation oncologist who wishes to understand the use of proton beam therapy (PBT) for locally advanced lung cancer. One randomized study is being performed and another is planned to clarify the differences in outcome for PBT compared to XRT. Newer forms of radiotherapy such as PBT should positively impact lung cancer patients." Sethi (2014) is a retrospective case series that assessed recurrence rates in 86 patients with retinoblastoma treated with PBT or photon radiotherapy. The 10-year cumulative incidence of RT-induced or in-field second

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			malignancies was significantly different between radiation modalities (proton vs photon: 0% vs 14%; P = .015). The 10-year cumulative incidence of all secondary malignancies was also different, although with borderline significance. Thanker (2014) is a time-driven activity-based costing study of two patients with advanced head and neck cancer treated with IMRT and intensity-modulated PBT. It is published in a non-peer-reviewed journal. Authors conclude that the episodic cost of care using IMPT was less costly and of higher value than IMRT. Yock (2014) is a case series that compared parent proxy health-related quality of life scores of 57 pediatric brain tumor patients treated with PBT with those of 63 pediatric brain tumor patients treated with photon beam radiation. The total core HRQoL score for the PRT-C, XRT-C, and normative population differed from one another and was 75.9, 65.4 and 80.9 respectively (p=0.002; p=0.024; p<0.001). HRQoL of pediatric brain tumor survivors

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			treated with PRT compares favorably to those treated with XRT and similar to healthy controls. The HTAS recommended coverage of PBT for pediatric tumors based on reviewing the limited evidence, expert testimony, and the lack of clinical equipoise that means future trials are unlikely to be conducted.
P	113	For further evidence, we highlight the multiple national guidelines that support the use of proton therapy. The National Comprehensive Cancer Network (NCCN) guidelines, the previously cited ASTRO model policy for proton therapy, and the model policy on coverage of proton beam therapy from the National Association of Proton Therapy (NAPT) both approve of the use of proton therapy for certain patients. The basis for these national guidelines is the growing body of evidence supporting the use of proton therapy for positive long-term treatment outcomes and quality of life for oncology patients. The weight of this evidence is reflected in the numerous Medicare contractors and private payors policies that provide coverage for PBT for a number of anatomical sites.	The guidelines cited are included in the CG document, with the exception of the NAPT. Staff were unable to identify guidelines via search of the NAPT website.
P	114	*PTCOG-NA urges you to* postpone finalizing *this coverage guidance and reconsider your methodology of reviewing clinical evidence. We offer the assistance of our clinical leadership to assist you with any review.*	Thank you for your comments.
P	115	Evidence on the Cost Effectiveness of PBT An overarching benefit of PBT versus photon therapy is its precise targeting that spares very sensitive adjacent normal tissue, resulting in reductions in toxicity and other negative occurrences post-treatment. We are very concerned that you failed to consider these benefits. A study published in *Cancer* [Mailhot Vega, RB et al, *Cancer* 2013] found that by avoiding years of costly side effects, PBT can be cost-effective for children with medulloblastoma.	Please see comment 13.
P	116	An example of this more comprehensive analysis is a recent study issued by MD Anderson Cancer Center and presented at the October 2014 meeting of PTCOG-NA (manuscript under development). The study found that the cost of PBT when used for accelerated partial breast irradiation to decrease overall treatment time and toxicity, was estimated at $13,833. Results of the study suggested that the cost of proton therapy is similar to other types of radiation.	Commenter references unpublished data; new published evidence will be considered as the CG enters re-review every 2 years.

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P	117	*PTCOG-NA strongly recommends that you include studies that consider cost of toxicity and other post-treatment conditions that can occur and which certainly impact costs and the quality of life of the patient.*	Thank you for your comments.
P	118	While we appreciate the opportunity to submit comments, we felt very limited in our ability to communicate to you due to the severe limitations on written (1000 word) and oral (3 minutes) comments. We believe the current process may stymie public input. *PTCOG-NA urges you to reconsider these guidelines.* Should you have any questions, please do not hesitate to contact me	Thank you for your comments.
Q	119	Dear Oregon HERC, I write this letter requesting your consideration in the coverage of proton therapy for prostate cancer.	Thank you for your comments.
Q	120	Proton therapy has been in clinical use in the US since the 1970s. There is a long track record establishing safety and efficacy in patients with prostate cancer over decades of experience. Due to the unique physical characteristics of proton beam radiation (PBT), proton therapy is associated with less dose to surrounding normal tissues in the pelvis (e.g. rectum, bladder) than photon/x-ray IMRT. It allows safe delivery of radiation to the prostate while minimizing side effects.	This is correct and consistent with the background information.
Q	121	Two phase III randomized studies established that protons are a safe and effective means to deliver dose-escalated radiotherapy, the current standard of care in prostate cancer. One study by Massachusetts General Hospital (MGH) randomized patients with prostate cancer to a higher dose proton boost versus lower dose x-ray boost to the prostate following pelvic radiation with xrays. (1) Another study by MGH and Lorna Linda randomized patients with prostate cancer to a higher dose versus lower dose proton boost in combination with x-ray radiation. (2) Both trials showed an improvement in local control with the higher dose proton boost with a very low risk of GU or GI complications.	References 1 and 2 are considered in the WAHTA report.
Q	122	A number of single institutional experiences have also reported excellent long term outcomes with proton therapy. Loma Linda reported a series of 1255 patients with prostate cancer treated with either protons or a combination of x-rays and protons. (3) Survival rates were excellent, and the risk of severe GU or GI complications was extremely low.	Reference 3 is a retrospective cohort study of 1255 patients treated with proton radiation therapy from 1991-1997. Authors concluded that disease-free survival rates were comparable with other forms of local therapy. Authors also concluded that "No difference was seen in toxicity between those treated with combined protons and photons (11 of 731) and those with protons alone (6

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			of 524; p = 0.52).
Q	123	More recently, University of Florida reported their 5-year control rates from 3 prospective PBT trials for prostate cancer: 99%, 99%, and 76% in low, intermediate, and high risk patients, respectively. Among 211 patients, only 1-2% experienced serious late toxicity. These results compare very favorably with published results for IMRT. (4)	Reference 4 is a report of three prospective trials encompassing 211 prostate cancer patients. The data on control rates are correct. Rates of grade 3 GI toxicity were 1.0% and rates of grade 3 urologic toxicity were 5.4%. Within-trial comparative data are not available; commenter is referencing historical IMRT data from other publications.
Q	124	An advantage of PBT is decreased exposure of normal pelvic tissues to low to moderate dose radiation (0-50 Gy). Low-dose radiation to pelvic structures is associated with bowel and bladder urgency, frequency, erectile dysfunction and secondary cancers. (5). These side effects can drastically influence a patient's quality of life (QOL).	Reference 5 is a retrospective questionnaire study of bowel, urinary, and sexual function in 65 patients who received external beam radiation therapy for localized prostate cancer. Within-trial comparative data are not available.
Q	125	No randomized, prospective studies exist comparing IMRT and PBT. Several attempted retrospective comparisons have been conducted using large, national databases including SEER, but these studies suffer from major weaknesses including lack of granular details on side effects such as rectal urgency, poor surrogates for measures of GI toxicity, and comparison based on historical cohorts of small numbers of patients treated with now outdated proton therapy techniques/technology. In one QOL study comparing men treated with IMRT versus PBT, there was less rectal urgency and frequency in men treated with PBT than IMRT. (6)	It is noted that prospective randomized studies exist. Reference 6 is a comparison of QOL data from two different cohort studies, 1243 men receiving PBT and 204 men receiving IMRT. There were **no differences in QOL summary scores** between the IMRT and PT cohorts during early follow-up (up to 2-years). Response to individual questions suggests

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			possible differences in specific bowel symptoms.
Q	126	Decreases in testosterone, the major male hormone responsible for sex drive and stamina, can adversely affect patient QOL. Minimizing low-dose radiation to the pelvis with PBT has been found to translate into improved ability to maintain normal testosterone levels in patients after treatment compared with x-rays. (7)	Reference 7 is included in the WAHTA report.
Q	127	Lastly, decreasing integral radiation dose to the body is associated with a reduced risk for secondary cancers. This is particularly important for younger men seeking an alternative to surgery. In a matched-cohort study that included 33% of men treated for prostate cancer, PBT led to a 50% reduction in incidence of secondary cancers compared to photon-based radiation. (8)	Reference 8 is included in the WAHTA report.
Q	128	We recognize the importance of generating high level-evidence confirming the benefits of PBT in prostate cancer treatment. We are participating in the ongoing multicenter "PartiQOL" randomized trial comparing IMRT vs protons for prostate cancer. Clinical trials like PartiQOL will help quantify the degree of improvement in patient-reported quality of life with PBT over IMRT. In addition, all of our prostate cancer patients are enrolled on a prospective multicenter clinical registry capturing patient reported QOL measures before and after treatment as well as disease control outcomes.	Studies in progress will be considered following publication.
Q	129	This need for continued clinical evidence development (CED) and comparative effectiveness data is recognized by the current ASTRO national model policy for PBT. (9) Under this policy, enrollment in an IRB approved multi-institutional patient registry that adheres to Medicare requirements for CED is considered an indication for proton therapy that should be covered by an insurance carrier. These important trials cannot not be completed if PBT is not covered.	Regarding ASTRO, please see comment 5. Regarding CED, please see comment J57.
R	130	To Whom It May Concern: This letter is in regards to the Oregon Health Evidence Review Commission coverage guidelines for proton beam therapy. As an assistant professor in the department of radiation oncology at the University of Washington, I sub-specialize in breast cancer and would like to comment on the use of proton beam therapy for breast cancer.	Thank you for your comments.
R	131	Proton beam therapy is currently being used in the treatment of breast cancer in many proton centers across the country. The largest, single-institution experience to date using proton beam therapy for breast cancer comes from Loma Linda, where at last publication in 2014, one hundred women with *early stage breast cancer* had been treated with proton beam therapy following surgery (lumpectomy) as part of breast-conserving therapy. (1) When compared with 3-dimensional conformal photon plans for partial breast irradiation, Bush *et al.* reported a significant reduction in exposure to surrounding normal breast tissue with proton beam therapy that led to improved cosmetic outcomes. (2) There was also nominally lower radiation dose to the lung and heart with proton.	Data from the Loma Linda trial are considered in the WAHTA report. Reference 1 was published after the WAHTA report and reports 5-year follow up data on this phase 2 trial of 100 patients; results are not significantly different from prior

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			publications.
R	132	More recently proton beam therapy has been investigated in *locally advanced breast cancer*. The initial experience from Massachusetts General Hospital was published in 2013 and reported on stage III breast cancer patients that were irradiated with protons after mastectomy to the chest wall and regional lymphatics. (3) A comparative dosimetric analysis between proton and photon plans demonstrated substantial reductions in both lung and heart exposure as defined by well-established metrics for those organs at risk. *In addition, there was improvement in prescription dose coverage to the areas at risk*, i.e. chest wall and regional lymphatics received adequate doses. (4) Acceptable acute toxicity (dermatitis and fatigue) was reported. A separate multi-institutional dosimetric study that compared treated photon/electron plans with created proton plans (in press for publication at the time of this letter) confirmed these findings and found superior chest wall and lymphatic coverage and superior normal tissue avoidance in the proton plans.	See comment A11.
R	133	Currently, there has been little experience in salvage or palliative treatment with proton beam therapy for breast cancer. However, future investigation of its use in the setting of local breast recurrence after previous breast conservation therapy (lumpectomy followed by radiotherapy) is worthwhile, particularly given that the current standard of care is mastectomy for these women. If repeat breast preservation can be safely achieved by utilizing proton beam therapy (via less repeat exposure to previously irradiated breast tissue), this can have a significant impact on quality of life.	No additional evidence is supplied.
R	134	No recent cost-effectiveness analyses exist for breast cancer treated with proton beam therapy. However, given the preliminary data described above including lower dose to the heart, lungs, without compromise of target volume coverage, there are potential savings associated with decreased long-term toxicity such as cardiac disease, lung disease and poor cosmetic outcomes. The draft coverage guidelines reference a Swedish study from 2005 that can serve as a guideline for future analyses, but an updated study with current costs in the United States and new information regarding radiation dose-effect relationships is necessary. Cost comparisons have been performed between proton beam therapy and alternative radiotherapy methods for accelerated partial breast irradiation, particularly single-entry catheter based systems that utilize high-dose rate brachytherapy as the radiation source. An up-to-date cost comparison can reveal whether there is still a cost advantage with proton beam therapy when using updated (lowered) reimbursement of single-entry catheter techniques.	No additional evidence is supplied.
R	135	In summary, I believe that the use of proton beam therapy for breast cancer is promising and has provided a significant benefit to the women we have treated. Many others will benefit from proton beam therapy when it becomes a standard treatment option.	Thank you for your comments.
S	136	Dear Oregon Health Evidence Review Commission: I am a board certified Radiation Oncologist on the faculty of the University of Washington and specialize in the treatment of gastrointestinal cancers. I am writing to you because I utilize	Thank you for your comments.

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		proton beam therapy (PBT) in select patients who may benefit from this technology. Patients with gastrointestinal cancers frequently require multimodality treatments (surgery, chemotherapy, radiation therapy) that are curative. However, these may come at the cost of significant early and late side effects that not only impact patients' quality of life but are also costly to health care systems. Key reasons why radiation therapy for gastrointestinal (GI) cancers is so toxic are the close proximity of critical normal GI organs and their high sensitivity to the damaging effects of radiation therapy.	
S	137	PBT has the unique property of eliminating exit radiation dose that patients would otherwise receive if treated with conventional x-rays. This is especially important in the gastrointestinal system where low to moderate doses of radiation to normal liver, stomach, and bowel cause numerous and potentially debilitating GI side effects, which include but not limited to nausea, vomiting, diarrhea, and liver failure.	This information is correct.
S	138	I urge the Commission to consider the following additional information and data when reviewing their coverage guidelines for GI cancers: Liver cancers In accordance with the recent ASTRO Model Policy for PBT, primary liver cancers are supported as medically necessary when treated in a hypofractionated regimen based on meeting the medical necessity requirements of PBT and on published clinical data. The liver is one of the most highly radiation sensitive organs in the body; low to moderate doses of radiation have a profound impact on the normal function of this organ, particularly when the liver is cirrhotic (scarred). PBT allows for safe radiation dose escalation to liver tumors, which has been shown in prospective studies to result in improve survival outcomes. (1)	Please see comment 5.
S	139	In addition to the prospective studies of PBT as detailed by the HERC, a recently published systematic review and meta-analysis compared data across 70 observational studies and demonstrated that compared to conventional photon radiotherapy, PBT had significantly superior 5-year overall survival (RR 25.9), progression-free survival (RR 1.86), and locoregional control (RR 4.3). (2) PBT also had significantly less severe acute and late toxicities (6.1% vs. 20% and 2.5% vs. 6.9%, respectively) compared to photon radiotherapy. Notably, hepatic toxicity, which is often highly morbid, life-threatening, and costly, was lower in PBT versus photon treated patients (3.1% vs. 9.9%).	Reference 2 is a systematic review and meta-analysis as described by the commenter. This was published after the WAHTA report. Carbon-ion therapy was included in the same group as PBT under the category of "charged particle therapy." Survival rates were better than conventional radiotherapy but similar to SBRT.
S	140	Furthermore, due to its dosimetric advantages, PBT allows for hypofractionated treatment, particularly for large liver	Commenter describes a scenario

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<tr><td></td><td></td><td>tumors that would not be amenable to conventional fractionation of photon radiotherapy: instead of delivering 40 fractions (8 weeks) of conventionally fractionated photon radiation, PBT can be safely delivered in only 15 fractions (3 weeks) with biologically equivalent doses. As shown in the table below, when using Medicare reimbursement rates (professional and technical fees), PBT results in cost savings of approximately 30% when compared to IMRT in this setting: $21,665.63 versus $30,678.93, respectively.
<table>
<tr><th colspan="2">IMRT (40 fractions)</th><th colspan="2">PBT (15 fractions)</th></tr>
<tr><td>1 New patient visit</td><td>99205</td><td>1 New patient visit</td><td>99205</td></tr>
<tr><td>1 Prescription</td><td>77263</td><td>1 Planning sim</td><td>77014</td></tr>
<tr><td>1 Sim</td><td>77290</td><td>1 Complex sim</td><td>77290</td></tr>
<tr><td>1 Verification sim</td><td>77280</td><td>1 3D sim</td><td>77295</td></tr>
<tr><td>1 IMRT plan</td><td>77301</td><td>1 Dosimetry calculations</td><td>77300</td></tr>
<tr><td>1 IMRT MLC Device</td><td>77338</td><td>1 Special dosimetry plan</td><td>77331</td></tr>
<tr><td>1 Immobilization Device</td><td>77334</td><td>4 Complex treatment devices</td><td>77334</td></tr>
<tr><td>8 Weekly mgmt</td><td>77427</td><td>4 Apertures/compensators</td><td>77334</td></tr>
<tr><td>8 Physics QA</td><td>77336</td><td>3 Physics QA</td><td>77336</td></tr>
<tr><td>40 IMRT treatments</td><td>G6015</td><td>2 Special physics consults</td><td>77370</td></tr>
<tr><td>6 Films</td><td>77417</td><td>Special treatment procedure</td><td>77470</td></tr>
<tr><td>7 Basic dosi calcs</td><td>77300</td><td>15 IGRT</td><td>G6002</td></tr>
<tr><td>40 CTs</td><td>77014</td><td>15 PBT treatments</td><td>77523</td></tr>
<tr><td>1 Follow-up visit</td><td>99213</td><td>1 Follow-up visit</td><td>99213</td></tr>
<tr><td>Total Cost</td><td>$30,678.93</td><td>Total Cost</td><td>$21,665.63</td></tr>
</table></td><td>in which higher doses can be delivered more efficiently with PBT for liver cancer; published citation is not provided and source of this table is not cited.</td></tr>
<tr><td>S</td><td>141</td><td>Pancreatic cancers

The Commission did not specifically include the review of evidence of PBT in pancreatic cancers. Radiation treatment with concurrent chemotherapy for pancreatic cancer is associated with significant GI toxicity. With conventional radiation, severe acute GI toxicities occur in up to 20% of patients, which can often be treatment-limiting and</td><td>WAHTA identified no comparative studies of the clinical effectiveness of primary PBT in gastrointestinal cancers. Pancreatic cancer data were</td></tr>
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		compromise full completion of treatment. (3)	considered under the category of gastrointestinal cancers. Recommendation is not to cover based on insufficient evidence.
S	142	Dosimetric data as well as phase I clinical data demonstrate that PBT for pancreatic cancer is feasible, tolerable, and safer than with photon therapy. A dosimetric analysis of proton and photon plans for the adjuvant treatment of pancreatic cancer from the University of Florida showed superior small bowel and stomach sparing with PBT. (4)	Commenter notes Phase I clinical data, which was not considered in the CG report. Evidence development for pancreatic cancer is ongoing and will be considered in future updates of the CG.
S	143	A phase I/II study of 50 patients with locally advanced pancreas cancer used 3 dose fractionation schemes of PBT depending on the location of the tumor in relation to other GI structures with concurrent. They found excellent efficacy compared to historical controls of locally advanced pancreas cancer (1-yr local progression free survival 82%, progression free survival 64%, overall survival 77%). (5) The toxicities were low compared to the above mentioned photon based regimens with acute Grade 3 and higher rates as follows: nausea/vomiting 8%, anorexia 8%, weight loss 5%, and fatigue 3%.	Reference 5 is considered in the WAHTA evidence review.
S	144	More recent data from University of Florida and University of Pennsylvania provide additional data that PBT is better tolerated than photons. Nichols et al. from University of Florida demonstrated no grade 3 toxicities or treatment interruptions due to toxicity in 22 patients treated with PBT and concurrent chemotherapy. (6) At the University of Pennsylvania, 13 patients with pancreatic cancer treated with concurrent chemotherapy and proton PBT were compared to a cohort of patients treated during the same time period with photon radiotherapy to similar doses: 24% of the photon patients experienced grade 3 toxicity, whereas only 8% of the PBT cohort had this grade of toxicity. (7)	Reference 6 is considered in the WAHTA evidence review. Reference 7 is a non-randomized comparative study of 13 patients who received proton chemoradiation therapy versus a concurrent cohort of 17 patients who received photon therapy. Rates of toxicity were similar.
S	145	*In summary, there are adequate data from multiple institutions that demonstrate the safety and efficacy of PBT for liver and pancreatic cancers. The reduction in treatment-related toxicities with PBT compared to photon treatment also has the potential to result in cost-savings in these challenging diseases. I urge the Commission to support the coverage of PBT for liver and pancreatic cancers. I welcome the opportunity to serve as an on-going resource as you are assessing*	Thank you for your comments.

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		this important cancer therapy option for Oregonians.	
T	146	In 2011, I was diagnosed with Non-Hodgkins's Lymphoma (NHL) of the Central Nervous System with a mass found per MRI and CT Scan in the L) parietal dura of the brain & inoperable). I was told this is a rare mass found in only 3% of the population of those with NHL. After numerous lumbar punctures and samples of spinal fluid, bone marrow biopsies and finally an Craniotomy for an open biopsy, I began mega dose chemotherapy over a nine month period. At completion and for 12 months I was considered in remission. But after 14 mo MRI check up, they discovered that the mass was returning. At that point, I was given my options of Radiation (radiotherapy with standard Photons) with all it's side affects that would probably include blood brain barrier penetration leaving me with possible irreversible neurological damages, not to mention the probable return of the mass again. There IS limited control with the use of the Photon beams.	Thank you for your comments.
T	147	Or I could endure another long regime of chemo, this time with IT therapy (Intrathecal). Of which there are often high grade toxicities of blood, liver or renal systems). Especially in folks over 60 years of age. Wow, what a choice! (NOT)	Thank you for your comments.
T	148	Then, trying to take all this in for a few days, and pretty much deciding not to do any more treatments, I received a call from my Neuro Oncologist at UW Med Center, stating he had just talked to a specialist at the SCCA Proton Center (new to Seattle about a year before) about my case (my mass was wide but very shallow) and the doctor was interested in using their newest form of therapy called Pencil Beam Scanning (the PBS had only been available for a couple of months at that time). He went on to explain that PBS is higher degree of precision of the Proton Beam with overall minimal exposure and radiation to healthy tissues surrounding the mass. So, I spoke with my family and doctors and decided to take a chance. Then I did my research and discovered that Proton Therapy has been around for 25 years in the U.S. and a few other countries and that it was shown to be effective in treating many types of tumors, including cancers of the brain, CNS, head, neck, prostrate, lung and GI system, as well as cancers that cannot be removed (or completely removed) by surgery or chemo. I was again hopeful.	Thank you for your comments.
T	149	You don't know what it means, or feels like to have someone tell you you're NOT going to have to do the intense treatments that make you feel miserable day after day, to miss family functions or not being able live your life as normally as you'd like.	Thank you for your comments.
T	150	Feb 10, 2014, the first day I entered the Proton Center in Seattle, I felt like I had 'come home' to a new family of folks who are there to help all their patients feel comfortable in their stress-free and friendly environment, as anywhere I had ever been. The team of radiologists were 'my' team and treated me with respect, humor and a positivity beyond belief. I felt I could share my concerns, emotions and joys with them all. I cried when I had finished my regime of treatments, knowing I wouldn't be seeing them every day again. By the way, my only side affects included some tiredness and hair loss of the area radiated (which has since grown back) and missing 'my team' !	Thank you for your comments.

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T	151	Well, that was a year ago, and after my MRI last week, I am still mass free and as my docs put it, I have a 'beautiful brain' once again. This would not be the case with the other choices given to me. My daily life during the treatment did not change and I continued to enjoy daily activities. I can also look forward to the fact that the protons therapy reduces a reoccurrence or secondary mass. I can also live without the thought of residual neurological side affects later in my life.	Thank you for your comments.
T	152	The facility itself is a 'step into the future' kinda place. The center meets all needs of their patients, not just the amenities of the building but the non medical support needed especially if you are away from home, including housing, transportation and entertainment in the area, etc. Always supportive in every way.	Thank you for your comments.
T	153	Being a retired nurse, I can honestly say I have never had a more positive medical experience than that of SCCA Proton Center in Seattle. Believe me, it's different when you're on the receiving end of medical care!	Thank you for your comments.
T	154	I have recommended it to those I know with medical issues that would benefit from Proton Therapy. I'm happy to say that their treatments and positive experiences have been the same as mine. We are blessed to have this 'state of the art' facility in our part of the country. The need is great for more compassionate and successful treatments of all types of cancers. It will definitely be the only way of doing radiation therapy in the near future.	Thank you for your comments.
T	155	I truly feel it would be a disgrace to deny countless lives, the quality (with nil side affects) and compassionate treatment found in Proton Therapy. Please consider SUPPORTING the use of Proton Therapy. It's here to stay. Maybe you would need it someday! Would you want it to be denied to you or a loved one? A true believer in compassionate and quality care!	Thank you for your comments.
U	156	Hello, I chose proton therapy because it has low risk of side effects such as incontinence, impotence and bowel urgency. I also chose proton therapy because I can go to work every day and work a full day's work. I have not missed a single day's work during my treatment. I have been able to perform my work normally with some minimal impact, such as some minor urinary urgency. I would absolutely recommend proton therapy for anyone for whom this is a valid therapy. The impact to my body has been minimal. The treatment here at the SCCA Proton Center in Seattle has been very professional, and my wife and I both felt very encouraged by the whole process, from intake through the daily treatments and the weekly meetings with nurses and my oncologist.	Thank you for your comments.

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V	157	Please support proton radiation for liver cancer and other cancer where less tissue damage is critical to success of treatment. Thank you	Thank you for your comments
W	158	Dear Oregon Health Evidence Review Commission: I am a Radiation Oncologist on the faculty of the University of Washington and Seattle Children's Hospital. A majority of my patients are children with cancer, and I treat more children with cancer than any other radiation oncologist in the Northwest. About half of my patients are from the Seattle area, and the other half come from other parts of Washington, Alaska, Oregon, Montana, Idaho, and British Columbia.	Thank you for your comments.
W	159	The lack of exit dose with proton radiation can be critical for providing the optimal radiation therapy for children with developing bodies. It allows the patient to receive the maximum efficacy of treatment with decreased acute and late effects. On 11 July 2014 the Washington Health Technology Assessment adopted its final decision to recommend universal coverage for pediatric cancers.	This information is correct.
W	160	Nonetheless the best modality of radiation for each patient is individually assessed. I have treated two children from Oregon with proton therapy; however; I have recently supported the decisions by local Oregon radiation oncologists to treat with photon therapy rather than have them travel for proton therapy.	Thank you for your comments.
W	161	I am a member of the Children's Oncology Group (COG), the principle US entity for clinical research about pediatric cancers. It is noteworthy that most clinical trials that call for radiation other than whole brain radiation (including trials for most brain, Ewings, and rhabdomyosarcoma) allow for the clinician to choose the modality of radiation-proton or photon; it is not a study question on any COG clinical trial.	Thank you for your comments.
W	162	It is also noteworthy that even in somewhat resource-constrained, more centrally organized health systems, proton therapy for pediatric patients is increasingly accepted. For example, Britain's National Health Service is constructing two proton facilities that will treat children.	This is correct.
W	163	It is rare for a pediatric patient not to receive insurance coverage for proton therapy, either with public or private insurance. I urge you to continue support for Oregon pediatric patients to receive proton therapy, particularly when there is consensus between the Oregon radiation oncologist and the proton radiation oncologist.	Thank you for your comments.
W	164	Other clinicians will focus on the benefits of treating lymphoma (including pediatric lymphomas) with proton therapy, therefore I will focus on pediatric head and neck and central nervous system tumors. Summary of Evidence for Pediatric head and neck and central nervous system cancers: Although children often survive their pediatric cancers, the long term morbidity of treatment, including radiation, can have dramatic effects on quality of life, which can be mitigated with proton therapy. Although the impact of radiation late effects is most obvious with central nervous system tumors, many of the same considerations apply when treating	Thank you for your comments.

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		pediatric cancers abutting or close to the central nervous system, such as rhabdomyosarcomas of the face and orbit.	
W	165	Among the many studies of pediatric patients receiving radiation therapy, some of the most relevant include. • Pediatric patients had improved short term morbidity when comparing a cohort of proton-treated patients with historical controls. (1) • Patients receiving irradiation for a brain tumor before than age of four, only a third of adult survivors were able to have full -time employment. (2) Modeling of proton therapy versus photon therapy showed decreased effect on neurocognitive development and pituitary ·function with proton therapy. (3) • Young children with ependymoma treated with protons showed patients exhibited remarkably few side effects in terms of hearing loss, neurocognitive effects, and pituitary dysfunction compared to historical controls. (4) • Children treated with protons for low grade gliomas showed almost no neurocognitive, endocrine or visual effects of the treatment in follow up. (5) • Children with retinoblastoma treated with photon radiation had a 14% 10 year cumulative incidence of secondary malignancies versus 0% in patients treated with protons. (6) • Using protons for craniospinal irradiation is likely to mitigate the future risk of breast cancer, ovarian failure, and hemi disease in adult survivors of embryonal brain tumors. (7-9) • Overall, when including future costs of late effects, *proton therapy will be cost-effective compared to photon therapy* for medulloblastoma. (10) • *Proton therapy will be cost-effective* based on growth hormone function preservation when it reduces dose to the hypothalamus (11)	Reference 1 was published after WAHTA and is a case series of 83 patients 21 years and younger treated 2009-2012, who were compared to historical controls. Authors conclude "In comparison to conventional therapy, patients with particle therapy do not suffer from increased acute treatment-related toxicity during the first months." References 2 and 3 are addressed above; please see comments 61 and 95. Reference 4 is considered in the WAHTA evidence review. Reference 5 was published after the WAHTA review and is a case series of 32 pediatric patients treated from 1995 to 2007. Authors conclude, "Proton RT appears to be associated with good clinical outcome, especially when the tumor location allows for increased sparing of the left temporal lobe, hippocampus, and hypothalamic-pituitary axis." Reference 6 was also published after the WAHTA review and is a retrospective comparative

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			cohort study of 55 proton and 31 photon patients. The 10-year cumulative incidence of RT-induced or in-field second malignancies was significantly different between radiation modalities (0% vs 14%). The 10-year cumulative incidence of all second malignancies was also different, although with borderline significance (5% vs 14%). Reference 7 is a treatment modeling study of six female patients that designed photon and proton beam plans to compare radiation dose to the breast. Dose to breast tissues was near zero after proton therapy to the spine. Reference 8 is another modeling study in which proton therapy is compared to oophoropexy followed by Xray craniospinal irradiation in a single patient. Reference 9 is addressed in comment 59. References 10 and 11 are addressed in comment 13. HTAS recommended coverage of pediatric malignant tumors.
W	166	Thank you for this opportunity. Should you have any questions please do not hesitate to contact me	Thank you for your comments.

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X	167	Hello, I would like to see Regence cover proton radiation therapy for all forms of cancer, or at least liver cancer where it has proven to be efficacious.	Commenter addresses Regence; nevertheless, thank you for your comments.
Y	168	On behalf of the National Association for Proton Therapy (NAPT), we respectfully submit comments on Oregon's Health Evidence Review Commission (HERC) Coverage Guidance on Proton Beam Therapy (PBT). While we were pleased to see the strong recommendation for coverage of malignant ocular tumors, we have significant concerns with many of the other recommendations. We were especially surprised and disappointed with the lack of a positive coverage recommendation for pediatric malignant tumors. Because of the strong evidence supporting its use, PBT for pediatric patients is practically universally covered. Additionally, we strongly disagree with your characterization that "PBT is far more expensive than its major alternatives." Recent studies have found that when treating for toxicity and other post-treatment occurrences are considered, PBT has been found to be a cost-effective treatment. We urge you to consider the evidence we provide in this letter in your deliberations. Evidence on the Effectiveness of PBT for Pediatric Malignant Tumors The proposed coverage guidance gave a weak recommendation for coverage for pediatric malignant tumors, despite the overwhelming consensus on its appropriateness for pediatric patients. We believe eliminating coverage of PBT for pediatric patients is inconsistent with the current state of evidence and would be harmful to a population of patients who would most benefit from the reduced amount of radiation received in the course of PBT treatment. Due to the growing body of evidence in this area, most payors, regulators and providers support the use of PBT for pediatric patients. The consensus is reflected in the American Society for Radiation Oncology (ASTRO) model policy on PBT which supports its use for primary or benign solid tumors treated in children with curative intent (ASTRO, 2014). Examples of published evidence in this area include a recent study of 54 patients with pediatric rhabdomyosarcoma which found that PBT lowers integral dose and improves sparing normal tissue when compared to IMRT [Ladra, MM et al Radiother Oncol 2014]. In another example, a 2012 study of high-risk pediatric neuroblastoma found that preliminary outcomes reveal excellent control with proton therapy for this population [Hattagangadi JA, Int J Radiat Oncol Biol Phys, 2012]. While we have cited just two studies, these are consistent with other studies of pediatric patients. Evidence on the Effectiveness of PBT for Other Sites The proposed guidance concludes, " ... there was insufficient evidence to obtain even a basic understanding of PBT' s comparative clinical effectiveness and comparative value." Frankly, we were stunned by this characterization. While we acknowledge (and support) the ongoing development of additional clinical evidence, there is already significant evidence supporting the effectiveness of PBT that this proposed coverage guidance ignores. In addition to the evidence	Identical letter to that submitted by commenter P; see responses above

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		supporting the use of PBT for pediatric tumors, there is also significant evidence supporting its use for other tumor sites. The articles listed below are only from the last 15 months and they reflect the meaningful research being conducted in this area. 2015 • Cuaron JJ, Chon B, Tsai H, Goenka A, DeBlois D, Ho A, Simon P, HugE, Cahlon 0 . Early toxicity in patients treated with postoperative proton therapy for locally advanced breast cancer. *Radiation Oncology.* Published online March 6, 2015. • Holliday EB, Mitra HS, Somerson JS, Rhines LD, Mahajan A, Brown PD, Grosshans DR. Postoperative proton therapy for chordomas and chondrosarcomas of the spine: adjuvant vs. salvage radiation therapy. *Spine.* Published online January 23, 2015. • Mizumoto M, Oshiro Y, Takizawa D, Fukushima T, Fukushima H, Yamamoto T, Muroi A, Okumura T, Koji T, Sakura H. Proton beam therapy for pediatric patients with ependymoma. *Pediatrics International.* 2015; DOI:10.1111/ped.12624. • Vega RM, Kim J, Hollander A, Hattangadi-Giuth J, Michalski J, Tarbell NJ, Yock Tl, Bussiere M, MacDonald SM. Cost effectiveness of proton versus photon radiation therapy with respect to the risk of growth hormone deficiency in children. *Cancer.* Published online January 29, 2015. 2014 • Brower *N,* Gans S, Hartsell WF, Goldman S, Fangusaro JR, Patel N, Lulla RR, Smiley NP, Change JH, Gondi V. Proton therapy and helical tomothrapy result in reduced dose deposition to the pancreas in the setting of cranio-spinal irradiation for medulloblastoma: implications for reduced risk of diabetes mellitus in long-term survivors. *Acta Oncol.* 2014 Nov: 1-5. • Frank SJ, Cox JD, Gillin M, Mohan R, Garden AS, Rosenthal DI, Gunn GB, Weber RS, Kies MS, Lewin JS, Munsell MF, Palmer MB, Sahoo N, Zhang X, Liu W, Zhu XR. Multifield optimization intensity modulated proton therapy for head and neck tumors: a translation topractice. *Int J Radiat Oncol Bioi Phys.* 2014 Jul 15;89(4):846-53. • Kesarwala AH, Ko CJ, Ning H, et al. Intensity-modulated proton therapy for elective nodal irradiation and involved-field radiation in the definitive treatment of locally advanced non-smallcell lung cancer: a dosimetric study. *Clinical Lung Cancer.* Available online 9 December 2014. Ladra MM, Szymonifka JD, Mahajan A, et al. Preliminary results of a phase II trial of proton radiotherapy for pediatric rhabdomyosarcoma. *J Clin Oncol.* 2014 Oct 20; epub ahead of print. • Ling TC, Slater JM, et al. Analysis of intensity-modulated radiation therapy (IMRT), proton and 3D conformal	

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		you failed to consider these benefits. A study published in *Cancer* [Mailhot Vega, RB et al, *Cancer* 2013] found that by avoiding years of costly side effects, PBT can be cost-effective for children with medulloblastoma. An example of this more comprehensive analysis is a recent study issued by MD Anderson Cancer Center and presented at the October 2014 meeting ofPTCOG-NA (manuscript under development). The study found that the cost of PBT when used for accelerated partial breast irradiation to decrease overall treatment time and toxicity, was estimated at $13,833. Results of the study suggested that the cost of proton therapy is similar to other types of radiation. *NAPT strongly recommends that you include studies that consider cost of toxicity and other post-treatment conditions that can occur and which certainly impact costs and the quality of life of the patient.* While we appreciate the opportunity to submit comments, we felt very limited in our ability to communicate to you due to the severe limitations on written (1000 word) and oral (3 minutes) comments. We believe the current process may stymie public input. *NAPT urges you to reconsider these guidelines.* Should you have any questions, please do not hesitate to contact me	

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Index of Comments by Cancer Type

Brain, spinal, and paraspinal tumors: G34, N93, N99-N102

Breast cancer: A10-A11, J63, R130-R135

Gastrointestinal cancers: S136-S145

Head and neck cancers (including skull base tumors): A8-A9, J62, L68-L82

Liver cancer: S; citizen comments D28, E29, F30, K66, O105, V157, X167

Lung cancer: H37-H48

Lymphomas: C21-C27, T146-T155

Pediatric cancers (e.g., medulloblastoma, retinoblastoma, Ewing's sarcoma): G33, J59-J61, M86-M87, N94-N98, P107-P111, W158-W166, Y168

Prostate cancer: A12, B15-B20, Q121-Q129, U156

No comments received: Bone tumors, Esophageal cancer, Gynecologic cancers, Ocular tumor, Soft tissue sarcomas, Seminoma, Thymoma, Noncancerous conditions, Arteriovenous malformations, Hemangiomas, Other benign tumors (e.g., acoustic neuromas, pituitary adenomas)

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