Health Evidence Review Commission's Value-based Benefits Subcommittee

February 2, 2017

8:00 AM - 1:00 PM

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
February 2, 2017
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. Pain Commission letter on use of the pain scale	
	B. Errata	
	C. Sacroiliac joint surgery final changes	
III.	**Advisory panel reports – Ariel Smits, Cat Livingston, Darren Coffman**	**8:15 AM**
	A. OHAP report	
IV.	**Straightforward/Consent agenda – Ariel Smits**	**8:25 AM**
	A. Consent table	
	B. Diaphragmatic hernia	
V.	**2018 Biennial Review**	**8:30 AM**
	A. Prioritization of pharmacologic treatments for Chronic Hepatitis C	
	B. Injuries to major blood vessels	
	C. Secondary and ill-defined malignancies	
VI.	**Break**	**10:40 AM**
VII.	**Coverage guidances**	**10:50 AM**
	A. Digital Breast Tomosynthesis (3D Mammography) for Breast Cancer Screening in Average Risk Women	
VIII.	**New discussion items**	**11:30 AM**
	A. Fecal microbiota transplant for recurrent C difficile infection	
	B. Gallstones	
	C. Meniscal injuries	
	D. Chronic otitis media with hearing loss	

IX.	**Previous discussion items** **A.** Preventive services guideline edits **B.** Bariatric surgery guideline	**12:30 PM**
X.	**Public comment**	**12:55 PM**
XI.	**Adjournment – Kevin Olson**	**1:00 PM**

Value-based Benefits Subcommittee Recommendations Summary
For Presentation to:
Health Evidence Review Commission on November 10, 2016

For specific coding recommendations and guideline wording, please see the text of the 11/10/2016 VbBS minutes.

RECOMMENDED CODE MOVEMENT (effective 1/1/17 unless otherwise noted)

- Delete residential mental health treatment from several inappropriate lines.
- Delete supportive employment and crisis intervention coders from the Prioritized List and place on the Ancillary File.
- Add the 2017 CPT and HCPCS codes to various lines and lists.
- Add the procedure code for sacroiliac joint fusion and the diagnosis code for sacroiliitis to an uncovered line with a new guideline note.
- Add coverage for diagnostic sacroiliac joint injections with a new guideline.
- Remove skin substitute codes from a deep open wound line.
- Add a dietary surveillance code to the obesity line.
- Add and delete various straightforward coding changes.

ITEMS CONSIDERED BUT NO RECOMMENDATIONS FOR CHANGES MADE

- The federal definition of habilitative was not added to the Rehabilitative and Habilitative Services Guideline.
- Higher prioritization was considered for uncomplicated inguinal hernias, but no changes were made.
- Confirm ongoing noncoverage of pharmacotherapy for obesity.

RECOMMENDED GUIDELINE CHANGES (effective 1/1/17 unless otherwise noted)

- Update the non-prenatal genetic testing guideline to include the most current NCCN guidelines.
- Add a new guideline regarding repair of paravalvular leaks.
- Edit the preventive services guideline to clarify that USPSTF “D” recommendations are included on the uncovered lower preventive services line.
- Edit the back surgery guideline to clarify coverage, including coverage of spinal fusion with cervical decompression for spondylolisthesis.
- Edit the guideline on noninvasive testing for liver fibrosis to exclude 3 tests.
- Delete the guideline note on liver elastography, as it was superceded by the new guideline on noninvasive testing for liver fibrosis.
- Add a new guideline note on skin substitutes for chronic skin ulcers.
- Modify the guideline on obesity and overweight to clarify coverage of behavioral interventions and add specific detail about children.
- Add language to the guideline on obesity to clarify non-coverage of devices for obesity and add them to the Services Recommended for Non-Coverage Table.

- Add a new multisector intervention statement on the prevention and treatment of obesity.
- Update the ventral hernia guideline to clarify the current noncoverage of repair.
- Add a new guideline clarifying that long-acting reversible contraceptives are covered in the postpartum and postabortion setting.

VALUE-BASED BENEFITS SUBCOMMITTEE
Clackamas Community College
Wilsonville Training Center, Rooms 111-112
Wilsonville, Oregon
November 10, 2016
8:00 AM – 1:00 PM

Members Present: Kevin Olson, MD, Chair; Susan Williams, MD, Vice-chair (by phone); David Pollack, MD; Mark Gibson; Irene Croswell, RPh; Holly Jo Hodges, MD (9:30 arrival); Vern Saboe, DC; Gary Allen, DMD.

Members Absent: None.

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

Also Attending: Jesse Little and Kim Wentz, MD, MPH, (Oregon Health Authority); Valerie King, MD MPH, Rachel Hackett, Craig Mosbaek, and Moira Ray, MD (OHSU Center for Evidence-based Policy); Duncan Neilson, MD; Maria Rodriquez, MD (via phone); Andy Kranenberg, MD (via phone); Jessie Payne; Margaret Olmon (Abbvie); Blair Elgren (Osiris); Grant Hamilton (SI-Bone); Duncan Neilsen, MD (Legacy Health Systems); Sara Love (CCO Oregon).

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

  The meeting was called to order at 8:00 am and roll was called. Minutes from the October 10, 2016 VbBS meeting were reviewed and approved. Staff pointed out edits to those minutes which were added after the packet was distributed, and these changes were considered appropriate.

  Smits reviewed the errata; there was no discussion.

  Coffman discussed the plan to have HERC review hepatitis C as a biennial review item. This topic was discussed in more detail at the later HERC meeting.

- **Topic: Genetics Advisory Panel (GAP) Report**

  Discussion: Smits reviewed the GAP report. There was some discussion about breast cancer gene panel testing. GAP had recommended that HERC staff review NCCN guidelines; staff reviewed this guideline and found no strong guidance. After staff conferred with HERC leadership, staff determined that there is no clear guidance but that this is a rapidly evolving field. The plan is to have GAP review this at their meeting next year. Smits also reviewed concerns raised about access to genetic counseling in the state. Pollack discussed the shortage of training programs in Oregon for genetic counseling. Olson noted that

genetic counselors are not licensed by the state and therefore cannot bill directly for their services. Lack of licensing is a barrier in Oregon. The need is increasing rapidly. VbBS requested that HERC make a motion to the staff of the health workforce or health policy board to license genetic counselors and workforce training. Workforce shortage impedes HERC's ability to implement evidence based guidelines around genetic testing.

The non-prenatal genetic testing guideline required straightforward changes to update the references to the most current NCCN guidelines.

The recommendations for 2017 CPT code placements involving genetic testing were approved as part of the larger 2017 code placements later in the meeting.

Recommended Actions:

1) Modify Diagnostic Guideline D1 as shown in Appendix A.

MOTION: To approve the guideline changes as presented. CARRIES 7-0. *(Absent: Hodges)*

- **Topic: Behavioral Health Advisory Panel (BHAP) Report**

Smits reviewed the BHAP report. There was minimal discussion. All coding changes recommended by BHAP were considered appropriate. VBBS agreed with the BHAP recommendation to not add acupuncture as a treatment for depression and to not continue to consider higher prioritization of insomnia for any age group.

The recommendations for 2017 CPT code placements related to behavioral health services were approved as part of the larger 2017 code placements later in the meeting.

Recommended Actions:

1) Remove HCPCS H0018 (Behavioral health; short-term residential (non-hospital residential treatment program) from the following lines:
    a. 153 FEEDING AND EATING DISORDERS OF INFANCY OR CHILDHOOD
    b. 216 NON-SUBSTANCE-RELATED ADDICTIVE BEHAVIORAL DISORDERS;
    c. 257 PSYCHOLOGICAL FACTORS AGGRAVATING PHYSICAL CONDITION (EG. ASTHMA, CHRONIC GI CONDITIONS, HYPERTENSION);
    d. 394 SEPARATION ANXIETY DISORDER;
    e. 397 PANIC DISORDER; AGORAPHOBIA;
    f. 419 OVERANXIOUS DISORDER; GENERALIZED ANXIETY DISORDER; ANXIETY DISORDER, UNSPECIFIED;
    g. 442 STEREOTYPY/HABIT DISORDER AND SELF-ABUSIVE BEHAVIOR DUE TO NEUROLOGICAL DYSFUNCTION;
    h. 466 OBSESSIVE-COMPULSIVE DISORDERS;
    i. 554 SOMATIC SYMPTOMS AND RELATED DISORDERS;
2) Remove H2023 (Supported employment, per 15 minutes) from all lines on the Prioritized List.

a. Advise HSD to place H2023 on the Ancillary File.

3) Remove H2011 (Crisis intervention service, per 15 minutes) from all lines on the Prioritized List.
    a. Advise HSD to place H2011 on the Diagnostic Workup File.
4) Add ICD-10 F50.89 (Other specified eating disorder) to line 153 FEEDING AND EATING DISORDERS OF INFANCY OR CHILDHOOD and line 635 PICA.
    a. Add a coding specification to lines 153 and 635 as follows:
        "ICD-10 F50.89 is included on lines 153 for avoidant/restrictive food intake disorder and on line 386 for psychogenic loss of appetite. ICD-10 F50.89 is included on line 635 for pica in adults and for all other diagnoses using this code."
5) Remove the following coding specification from line 386:
    ~~"ICD-10-CM F50.8 is included on this line only for binge eating disorder. All other diagnoses using this code (i.e. pica in adults) are included on line 664 PICA."~~

MOTION: To approve the coding changes as presented. CARRIES 7-0. *(Absent: Hodges)*

- **Topic: Straightforward/Consent Agenda**

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

Recommended Actions:

1) Add CPT 29822 (Arthroscopy, shoulder, surgical; debridement, limited) to line 157 PYOGENIC ARTHRITIS.
2) Add CPT 29821 (Arthroscopy, shoulder, surgical; synovectomy, complete) to line 406 BENIGN CONDITIONS OF BONE AND JOINTS AT HIGH RISK FOR COMPLICATIONS.
3) Add ICD-10 B69.0 (Cysticercosis of central nervous system) to line 338 BENIGN CEREBRAL CYSTS.
4) Add CPT 37212 (Transcatheter therapy, venous infusion for thrombolysis, any method, including radiological supervision and interpretation, initial treatment day) to line 51 DEEP ABSCESSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS.
5) Add CPT 38747 (Abdominal lymphadenectomy, regional, including celiac, gastric, portal, peripancreatic, with or without para-aortic and vena caval nodes) to line 321 CANCER OF PANCREAS.
6) Add CPT 15100 (Split-thickness autograft, trunk, arms, legs; first 100 sq cm or less, or 1% of body area of infants and children) to line 205 CANCER OF BONES.
7) Add CPT 67917 (Repair of ectropion; extensive (eg, tarsal strip operations)) to line 280 CANCER OF SKIN, EXCLUDING MALIGNANT MELANOMA.
8) Add CPT 21230 (Graft; rib cartilage, autogenous, to face, chin, nose or ear) and 21235 (Graft; ear cartilage, autogenous, to nose or ear (includes obtaining graft)) to line 280 CANCER OF SKIN, EXCLUDING MALIGNANT MELANOMA.
9) Add CPT 77293 (Respiratory motion management simulation) to line 321 CANCER OF PANCREAS.

10) Add CPT 43266 (Esophagogastroduodenoscopy, flexible, transoral; with placement of endoscopic stent (includes pre- and post-dilation and guide wire passage, when performed)) to line 220 CANCER OF STOMACH.
11) Add CPT 31600 (Tracheostomy, planned) to line 205 CANCER OF BONES.
12) Add CPT 38720 (Cervical lymphadenectomy (complete)) and 38724 (Cervical lymphadenectomy (modified radical neck dissection)) to line 205 CANCER OF BONES.
13) Add CPT 38760 (Inguinofemoral lymphadenectomy, superficial, including Cloquet's node) to line 291 CANCER OF VAGINA, VULVA, AND OTHER FEMALE GENITAL ORGANS.
14) Add CPT 77789 (Surface application of low dose rate radionuclide source) to line 117 CANCER OF EYE AND ORBIT.
15) Add CPT 49203-49205 (Excision or destruction, open, intra-abdominal tumors, cysts or endometriomas, 1 or more peritoneal, mesenteric, or retroperitoneal primary or secondary tumors…) to line 219 CANCER OF KIDNEY AND OTHER URINARY ORGANS.
16) Add CPT 78816 (Positron emission tomography (PET) with concurrently acquired computed tomography (CT) for attenuation correction and anatomical localization imaging; whole body) to line 117 CANCER OF EYE AND ORBIT.
17) Add Line 117 CANCER OF EYE AND ORBIT to Guideline Note (GN) 19 PET SCAN GUIDELINES.
18) Add CPT 21210 (Graft, bone; nasal, maxillary or malar areas (includes obtaining graft)) to line 305 CLEFT PALATE AND/OR CLEFT LIP.
19) Remove ICD-10 M11.8 (Other specified crystal arthropathies) from line 663 MUSCULOSKELETAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY and add to line 501 CALCIUM PYROPHOSPHATE DEPOSITION DISEASE (CPPD) AND HYDROXYAPETITE DEPOSITION DISEASE.
20) Add ICD-10 M13.87 (Other specified arthritis, ankle and foot) to line 361 RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, OSTEOCHONDRITIS DISSECANS, AND ASEPTIC NECROSIS OF BONE.
21) Add ICD-10 M24.17 (Other articular cartilage disorders, ankle or foot) to lines 361 RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, OSTEOCHONDRITIS DISSECANS, AND ASEPTIC NECROSIS OF BONE, 364 DEFORMITY/CLOSED DISLOCATION OF MAJOR JOINT AND RECURRENT JOINT DISLOCATIONS, and 467 OSTEOARTHRITIS AND ALLIED DISORDERS and remove from lines 392 DEFORMITY/CLOSED DISLOCATION OF MINOR JOINT AND RECURRENT JOINT DISLOCATIONS and 436 INTERNAL DERANGEMENT OF KNEE AND LIGAMENTOUS DISRUPTIONS OF THE KNEE, RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT.
22) Add ICD-10 M24.87 (Other specific joint derangements of ankle, not elsewhere classified) to lines 361 RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, OSTEOCHONDRITIS DISSECANS, AND ASEPTIC NECROSIS OF BONE and 467 OSTEOARTHRITIS AND ALLIED DISORDERS and remove from line 545 DEFORMITIES OF FOOT.
23) Add ICD-10 M25.87 (Other specified joint disorders, ankle and foot) to lines 361 RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, OSTEOCHONDRITIS DISSECANS, AND ASEPTIC NECROSIS OF BONE, 364 DEFORMITY/CLOSED DISLOCATION OF MAJOR JOINT AND RECURRENT JOINT DISLOCATIONS, and 467 OSTEOARTHRITIS AND ALLIED

DISORDERS and remove from line 530 DEFORMITIES OF UPPER BODY AND ALL LIMBS~~545 DEFORMITIES OF FOOT~~

24) Add ICD-10 A04.9 (Bacterial intestinal infection, unspecified) to line 664. GASTROINTESTINAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY and remove from line 150 ENTERIC INFECTIONS AND OTHER BACTERIAL FOOD POISONING.
25) Add ICD-10 K90.9 (Intestinal malabsorption, unspecified) to line 555 OTHER NONINFECTIOUS GASTROENTERITIS AND COLITIS an remove from line 232 INTESTINAL MALABSORPTION
26) Modify Guideline Note 24 as shown in Appendix A.

MOTION: To approve the recommendations stated in the consent agenda. CARRIES 7-0.
(Absent: Hodges)

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- **Topic: 2017 CPT/HCPCS Code Placements**

Discussion: There was no discussion about any of the CPT or HCPCS code placements with the following exceptions:

1) 58674 (Laparoscopy, surgical, ablation of uterine fibroid(s) including intraoperative ultrasound guidance and monitoring, radiofrequency) was felt to not be experimental. However, the recommended placement on the Services Recommended for Non-Coverage was felt to be appropriate. The rationale for placement should be insufficient level of effectiveness.

2) 77065-77067 (Diagnostic and screening mammography with computer-aided-detection): The subcommittee determined that the computer aided detection guideline should be maintained, with wording altered to remove the CPT codes. This may allow value-based pricing by HSD, and serves as a statement of HERC's assessment of the evidence around CAD.

3) G9678 (Oncology care model (ocm) monthly enhanced oncology services (meos) payment for ocm enhanced services) was added to the Ancillary list rather than the chemotherapy/radiation therapy lines.

Recommended Actions:

1) 2017 CPT and HPCS codes placements as shown in Appendix B.
2) Guideline note 106 was modified as shown in Appendix A.
3) Diagnostic Guideline D15 was modified as shown in Appendix A.
4) A new guideline was adopted regarding transcutaneous repair of paravalvular leaks as shown in Appendix C

MOTION: To approve the amended recommendations for code placement and guideline changes and new guideline. CARRIES 8-0.

- **Topic: Rehabilitative and Habilitative Therapy Guideline**

  Discussion: Smits reviewed the OHP medical director request to include the federal definition of habilitative in GN6. This definition is from federal rule and the subcommittee determined that it should not be included in the guideline. Therefore no changes should be made to the current guideline. HERC staff will direct health plans and providers with questions to the federal rule.

  MOTION: To make no changes to the guideline. CARRIES 8-0.

- **Topic: Back Surgery Guideline**

  Discussion: Smits introduced the summary document on back surgery guideline changes. Williams requested that the work "joint" be changed to "joints" in the criteria for spinal instability, as resection of one joint would not cause instability. Hodges asked how spinal instability would be determined by a medical director for determination of coverage; Williams indicated that the surgeon should document existing or expected instability in the pre-operative note.

  Recommended Actions:
  1) GN37 was modified as shown in Appendix A

  MOTION: To approve the guideline note changes as amended. CARRIES 8-0.

- **Topic: Non-invasive Tests for Liver Fibrosis**

  Discussion: Livingston presented the issue summary which would add to the guideline note on noninvasive testing of liver fibrosis that 3 tests are not included on any line on the Prioritized List (real time tissue elastography, Hepascore® (FibroScore®), and FibroSure® (FibroTest®). Olson let the group know that Providence is newly using Fibrosure®. Hodges asked a clarifying question about the deletion of guideline note 76. Livingston stated it was superseded by language adopted from the Coverage Guidance box language.

  Recommended Actions:
  1) Modify GUIDELINE NOTE XXX DIAGNOSTIC TESTING FOR LIVER FIBROSIS TO GUIDE TREATMENT OF HEPATITIS C IN NON-CIRRHOTIC PATIENTS as shown in Appendix A.
  2) Delete GUIDELINE NOTE 76, LIVER ELASTOGRAPHY as shown in Appendix D.

  MOTION: To approve the guideline note changes. CARRIES 8-0.

- **Topic: SI Joint Fusion**

Discussion: Smits reviewed the discussion on this topic from August, and the interim work done by HERC staff, Vern Saboe and Susan Williams. This work included the development of a possible guideline in SI joint fusion was added to the Prioritized List.

Andy Kranenberg, MD (via phone) testified, noting that he receives reimbursement for teaching the surgical technique to other providers, but does not have financial interest in the company. His testimony summarized the handout he provided to members, and involved the need for the SI joint fusion procedure and the evidence supporting this procedure. SI joint pain is disabling and has large impact on quality of life (QOL), and surgery can improve QOL and allows patients to continue working. Projected savings are sizable for using this procedure. He is in support of coverage with a guideline note similar to proposed. He went through the importance of treatment and the evidence supporting efficacy of the SI joint fusion procedure.

Jessie Payne, a patient who had SI joint fusion surgery, testified about her experience with SI joint pain, and the impact of this condition on her quality of life. She did multiple treatments, including physical therapy, chiropractic~~,~~ and acupuncture.~~-~~ After having the fusion done bilaterally as outpatient surgery, she was able to return to a high level of activity, and had a significant improvement in quality of life.

Pollack asked for further information on why the staff assessment of the evidence quality conflicts with the expert opinion on the evidence. Smits reviewed the evidence reviewed from August. Pollack asked if other experts such as physiatrists had been consulted. Staff indicated that no physiatrists had been consulted.

Saboe stated that the national chiropractic association review has found that the evidence does not support use. However, the evidence does show that a subset of individuals can benefit from surgery, and he thinks that the proposed guideline note would help define this group.

Olson summarized that the proposed guideline addresses the ability to accurately diagnose SI joint dysfunction and assists in identifying the subset of patients who could benefit from surgery.

Drs. Kranenberg and Williams indicated that SI joint anesthetic injection was an important part of the ability to correctly diagnose that SI joint dysfunction was the cause of the pain and that the North American Spine Association (NASS) guideline included a requirement for a good response to two separate anesthetic injections. They recommended including this clause in the guideline. Kranenberg indicated that the evidence does not support the use of corticosteroid injections as a stand along therapy for SI joint dysfunction, but the diagnostic injections are supported by evidence and expert guidelines. Staff indicated that the possible

CPT codes used for diagnostic SI joint injection were either Services Recommended for Non Coverage (i.e. 27096 Injection procedure for sacroiliac joint, anesthetic/steroid, with image guidance (fluoroscopy or CT) including arthrography when performed), or not on the back surgery line (i.e. 20610 Arthrocentesis, aspiration and/or injection, major joint or bursa (eg, shoulder, hip, knee, subacromial bursa); without ultrasound guidance or 20552 Injection(s); single or multiple trigger point(s), 1 or 2 muscle(s)). Staff was directed to determine the most appropriate CPT code for this injection type, and to add this code to the diagnostic list with a new diagnostic guideline that would clearly state that only the diagnostic injection is included for diagnostic coverage; the therapeutic steroid injection is not covered.

There was discussion about whether this procedure should be on the covered or on the uncovered back surgery line. If on the unfunded line, what comorbid conditions should be allowed? The thought was that if the pain interfered with exercise for control of diabetes or similar types of comorbid conditions, then it should be considered. Back pain should not be considered for a comorbid condition that would allow coverage of the SI joint surgery. There was discussion about adding to the upper covered line and requiring there to be significant disability from the condition. Livingston reviewed the major diagnoses on the covered surgical line such as myelopathy and spinal instability. SI joint dysfunction was felt to be more appropriate to be prioritized with the conditions on the lower surgical line. The decision was made to add the procedure and diagnosis codes to the lower back surgery line.

The proposed guideline was reviewed. References to pain values on pain scales were removed as the subcommittee felt that the patient should have function issues to qualify for surgery rather than just pain. There was discussion about removing the clause not allowing surgery for patients with other generalized pain conditions such as fibromyalgia. This was not adopted as the subcommittee felt that the NASS guideline should be followed for this clause. An additional clause was added based on the NASS requirement for good response to the diagnostic SI joint injection.

Recommended Actions:
1) Add CPT 27279 (Arthrodesis, sacroiliac joint, percutaneous or minimally invasive (indirect visualization), with image guidance, includes obtaining bone graft when performed, and placement of transfixing device) to 532 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS
2) Add ICD-10 M46.1 (Sacroiliitis, not elsewhere classified) to 532 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS and keep on line 407 CONDITIONS OF THE BACK AND SPINE
3) Adopt the a new guideline regarding sacroiliac joint fusion for line 532 as shown in appendix C
4) HERC staff to identify the correct CPT code(s) for diagnostic SI joint injection and place this/these code(s) on the Diagnostic List
5) Adopt a new diagnostic guideline regarding this diagnostic SI joint injection with HERC staff to determine the CPT code to place into this guideline as identified in #4 above. This guideline is shown in appendix C

Addendum: HERC staff identified the following codes as utilized for diagnostic SI joint injection:

1) *20610 Arthrocentesis, aspiration and/or injection, major joint or bursa (eg, shoulder, hip, knee, subacromial bursa); without ultrasound guidance*
2) *27096 Injection procedure for sacroiliac joint, anesthetic/steroid, with image guidance (fluoroscopy or CT) including arthrography when performed*

CPT 20610 is on various lines on the Prioritized List and is not a candidate for the Diagnostic List. HERC staff, in consultation with HERC leadership, placed these codes on line 532 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS. The new guideline initially approved as a diagnostic guideline was converted to a guideline attached to line 532 and merged with the SI joint fusion guideline. Minor wording changes were made to the text of this ~~is~~ guideline to improve clarity and allow this conversion.

MOTION: To approve the code changes and new guideline notes as modified and newly proposed. CARRIES 8-0.

- **Topic: Skin substitutes for chronic skin ulcers**

Discussion: Livingston presented the issue summary. There was minimal discussion. Olson asked for public comment. There was none. Williams asked for clarity around the reasons for not including brands of skin substitutes. Livingston addressed some of the issues with the rapidly evolving literature base. Hodges clarified that the paragraph at the end of the guideline note would be helpful in determining those with evidence and the least costly option.

Recommended Actions:

1) Remove skin substitute codes (CPT codes 15271-15278) from Line 212 DEEP OPEN WOUND, WITH OR WITHOUT TENDON OR NERVE INVOLVEMENT
2) Adopt a new guideline note on skin substitutes for chronic skin ulcers as shown in Appendix C.

MOTION: To approve the recommendations as stated in the issue summary. CARRIES 8-0.

- **Topic: Obesity Taskforce (Biennial Review)**

Discussion: Livingston presented the Obesity Task Force issue summaries on behavioral interventions for obesity, pharmacotherapy for obesity, and devices for obesity. There was minimal discussion. Mosbaek presented the evidence review on Multisector Interventions for Obesity. Pollack talked about the importance of having physicians in training having more experience with food and the social determinants of health. There was a discussion

about whether the multisector intervention statement should be specifically attached to the obesity and diabetes lines. Coffman discussed the issue with yoga coverage - that if there is a specific link to lines there may be unintended expectation that the multisector interventions are discretely covered services.

Staff was asked to see if there was a way to reference the obesity and diabetes line with multisector interventions.

Subcommittee members discussed that the audience of the multisector interventions is wider than the general Prioritized List changes. That the goal is to ensure public policy entities are aware of the evidence-based interventions. The group wondered about the public entities who may be interested in these topics and Olson discussed mentioning this further at HERC.

Recommended Actions:

1) Approve the Obesity Task Force Package on behavioral interventions, pharmacotherapy, and devices for overweight and obesity to the January, 2018 Prioritized List.
    a. Add Z71.3 Dietary counseling and surveillance to Line 325
    b. Delete the lower obesity line
    c. Modify guideline note 5 on behavioral interventions for obesity and overweight as shown in Appendix A
    d. Modify guideline note 5 to add language about intended noncoverage of devices for obesity as shown in Appendix A
    e. Add an entry to the Services Recommended for Non-Coverage table for devices for obesity
    f. Make no change to the current noncoverage of pharmacotherapy for obesity
    g. Add a Multisector Intervention statement on the prevention and treatment of obesity to the Prioritized List as shown in Appendix C

MOTION: To approve the Obesity Task Force package. CARRIES 8-0.

- **Topic: Repair of inguinal and ventral hernias**

Discussion: Smits reviewed the literature update on the comparative effectiveness and harms of watchful waiting versus elective repair of asymptomatic or minimally symptomatic inguinal hernias. The subcommittee discussed whether the evidence of improvement in quality of life (QOL) with elective repair justified adding coverage for non-symptomatic inguinal hernias. There was discussion about whether to add coverage for non-incarcerated/non-obstructed inguinal hernias that affected function or ability to be employed. It was noted that elective hernia repair is among the most common elective surgeries performed. No evidence was found that surgery improves function, but likely this

is due to the fact that most surgery is performed for pain prior to functional impairment. Pain does not appear to be related to risk of complications such as incarceration or obstruction. The decision was to make no change in coverage for inguinal or ventral hernia.

MOTION: To not recommend changes to current coverage of inguinal or ventral hernias CARRIES 8-0.

- **Topic: Coverage Guidance— Long acting reversible contraceptives (LARC)**

Discussion: Ray reviewed the Draft Coverage Guidance on LARC, including the evidence, the policy landscape, and public comments. Gibson asked about the difference in expulsion rates in the studies versus in the community. Ray clarified that there may be overestimates of community expulsion rates and some of the differences depended on postpartum versus postabortion groups.

Neilson stated that the major concern about coverage of LARC is about the global OB payment. The cost of LARC is prohibitive for hospitals to build this in as a part of their global payment for a delivery.

Olson clarified intent is to cover LARC placement in these circumstances and that administrative barriers should not serve as barriers to prevent their use.

VbBS members agreed that they would like to endorse the attached letter from Dr. Saha and Dr. Chan about the implementation challenges associated with LARC placement.

Hodges asked about making the reference materials readily available to the medical directors. Subcommittee members discussed various ways that these reference materials (specifically the CMS summary of solutions state Medicaid agencies have identified) should be readily available to medical directors. Staff was given leeway to determine the most effective way to make these available as part of the guideline note.

Recommended Actions:

1) Adopt a new guideline note on LARC placement as shown in Appendix C
2) Endorse the letter written by Dr. Saha and Dr. Chan to the plan Medical Directors
3) Staff to determine how to make the reference materials (solutions to administrative barriers) readily available to medical directors and clear on the Prioritized List

MOTION: To approve the recommended changes to the Prioritized List based on the draft Timing of LARC Placement Coverage Guidance. CARRIES 8-0.

- **Public Comment:**

  No additional public comment was received.

- **Issues for next meeting:**

  No items were carried forward to the next meeting

- **Next meeting:**

  January 12, 2017 at Clackamas Community College, Wilsonville Training Center, Wilsonville Oregon, Rooms 111-112.

- **Adjournment:**

  The meeting adjourned at 1:10 PM.

Appendix A
Revised Guideline Notes

DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE

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 V2.2016 (9/26/16) ~~V.1.2015 (5/4/15).~~ www.nccn.org.
      b) Breast and ovarian cancer syndrome genetic testing services (CPT 81162, 81211-81217) 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. V1.2017 (9/19/16). ~~V2.2015 (6/25/15).~~ www.nccn.org.

c) Breast and ovarian cancer syndrome genetic testing services (CPT 81162, 81211-81217) 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. V1.2017 (9/19/16). ~~V2.2015 (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. V2.2016 (9/26/16) ~~V.1.2015 (5/4/15).~~ 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 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)
      CFTR, cystic fibrosis transmembrane conductance regulator tests. CPT 81220, 81222, 81223: 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; introm 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 81221, 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. Genetic testing of the anpha-1 phenotype test is appropriate if 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) CPT 81412 Ashkenazi Jewish carrier testing panel: panel testing is only covered when the panel would replace and would be similar or lower cost than individual gene testing including CF carrier testing.

* 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

DIAGNOSTIC GUIDELINE D15, COMPUTER-AIDED MAMMOGRAPHY

Computer-aided mammography ~~(CPT code 77051 and 77052)~~ is not intended to be a covered service.

GUIDELINE NOTE 24, COMPLICATED HERNIAS

Lines 172,527

Complicated hernias are included on Line 172 if they cause symptoms of intestinal obstruction and/or strangulation. Incarcerated hernias (defined as non-reducible by physical manipulation) are also included on Line 172, excluding incarcerated ventral hernias. Incarcerated ventral hernias are included on Line 527, because the chronic incarceration of large ventral hernias does not place the patient at risk for impending strangulation.

Appendix A
Revised Guideline Notes

GUIDELINE NOTE 37, SURGICAL INTERVENTIONS FOR CONDITIONS OF THE BACK AND SPINE OTHER THAN SCOLIOSIS

Lines 351,532

~~Surgical consultation/consideration for surgical intervention are included on these lines only for patients with neurological complications, defined as showing objective evidence of one or more of the following:~~

- ~~A. Markedly abnormal reflexes~~
- ~~B. Segmental muscle weakness~~
- ~~C. Segmental sensory loss~~
- ~~D. EMG or NCV evidence of nerve root impingement~~
- ~~E. Cauda equina syndrome~~
- ~~F. Neurogenic bowel or bladder~~
- ~~G. Long tract abnormalities~~

Spondylolisthesis (ICD-10-CM M43.1, Q76.2) is included on Line 351 to pair only when it results in spinal stenosis with signs and symptoms of neurogenic claudication. Otherwise, these diagnoses are included on Line 532. Decompression and fusion surgeries are both included on these lines for spondylolisthesis.

Surgical correction of spinal stenosis (ICD-10-CM M48.0) is only included on Line 351 for patients with:

1) MRI evidence of moderate to severe central or foraminal spinal stenosis AND
2) A history of neurogenic claudication, or objective evidence of neurologic impairment consistent with MRI findings. Neurologic impairment is defined as objective evidence of one or more of the following:
    a) Markedly abnormal reflexes
    b) Segmental muscle weakness
    c) Segmental sensory loss
    d) EMG or NCV evidence of nerve root impingement
    e) Cauda equina syndrome
    f) Neurogenic bowel or bladder
    g) Long tract abnormalities

Otherwise, these diagnoses are included on Line 532. Only decompression surgery is included on these lines for spinal stenosis; spinal fusion procedures are not included on either line for ~~this diagnosis~~ spinal stenosis unless:

1) the spinal stenosis is in the cervical spine OR
2) spondylolisthesis is present as above OR
3) there is pre-existing or expected post-surgical spinal instability (e.g. degenerative scoliosis >10 deg, >50% of foraminal joints expected to be resected)

Appendix A
Revised Guideline Notes

The following interventions are not included on these lines due to lack of evidence of effectiveness for the treatment of conditions on these lines, including cervical, thoracic, lumbar, and sacral conditions:

- facet joint corticosteroid injection
- prolotherapy
- intradiscal corticosteroid injection
- local injections
- botulinum toxin injection
- intradiscal electrothermal therapy
- therapeutic medial branch block
- sacroiliac joint steroid injection
- coblation nucleoplasty
- percutaneous intradiscal radiofrequency thermocoagulation
- radiofrequency denervation
- epidural steroid injections

GUIDELINE NOTE 5, OBESITY AND OVERWEIGHT

Line 325

Medical treatment of overweight (with known cardiovascular risk factors) and obesity in adults is limited to ~~accepted~~ intensive~~,~~ counseling on nutrition and physical activity, provided by health care professionals. Intensive counseling is defined as face-to-face contact more than monthly. A multidisciplinary team is preferred, but a single clinician could also deliver intensive counseling in primary care or other settings.

~~Visits are not to exceed more than once per week.~~ Intensive counseling visits ~~(once every 1-2 weeks)~~ are included on this line for 6 months. Intensive counseling visits may continue for an additional 6 months (up to 12 months) as long as there is evidence of continued weight loss or improvement in cardiovascular risk factors based on the intervention. Maintenance visits at the conclusion of the intensive treatment are included on this line no more than monthly after this intensive counseling period. The characteristics of effective behavioral interventions include: high intensity programs; multicomponent (including at a minimum diet and exercise), group-based commercial programs; Mediterranean diet; and the following sub-elements -- calorie counting, contact with a dietician, and comparison to peers.

Known cardiovascular risk factors in overweight persons for which this therapy is effective include: hypertension, dyslipidemia, prediabetes~~impaired fasting glucose~~, or the metabolic syndrome.

Medical treatment of obesity in children is limited to comprehensive, intensive behavioral interventions. For treatment of children up to 12 years old, interventions may be targeted only to parents, or to both parents and children.

Appendix A
Revised Guideline Notes

Pharmacological treatments and devices (e.g. gastric balloons, duodenal jejunal bypass liners, and vagus nerve blocking devices) for obesity are not intended to be included as services on this line or any other line on the Prioritized List.

GUIDELINE NOTE 106, PREVENTIVE SERVICES

Line 3,625

Included on ~~this~~ line 3 are the following preventive services as required by federal law:

1. US Preventive Services Task Force (USPSTF) "A" and "B" Recommendations
   http://www.uspreventiveservicestaskforce.org/Page/Name/uspstf-a-and-b-recommendations/
2. American Academy of Pediatrics (AAP) Bright Futures Guidelines:
   http://brightfutures.aap.org. Periodicity schedule available at
   http://www.aap.org/en-us/professional-resources/practice-support/Periodicity/Periodicity%20Schedule_FINAL.pdf.
3. **Health Resources and Services Administration (HRSA) Women's Preventive Services - Required Health Plan Coverage Guidelines:**
   http://www.hrsa.gov/womensguidelines/
4. Immunizations as recommended by the Advisory Committee on Immunization Practices (ACIP):
   http://www.cdc.gov/vaccines/schedules/hcp/index.html

USPSTF "D" recommendations are included on line 625

Code	Description	Placement
22853	Insertion of interbody biomechanical device(s) (eg, synthetic cage, mesh) with integral anterior instrumentation for device anchoring (eg, screws, flanges), when performed, to intervertebral disc space in conjunction with interbody arthrodesis, each inter	51 DEEP ABSCESSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS 154 CERVICAL VERTEBRAL DISLOCATIONS/FRACTURES, OPEN OR CLOSED; OTHER VERTEBRAL DISLOCATIONS/FRACTURES, OPEN OR UNSTABLE; SPINAL CORD INJURIES WITH OR WITHOUT EVIDENCE OF VERTEBRAL INJURY 205 CANCER OF BONES 259 CHRONIC OSTEOMYELITIS 351 CONDITIONS OF THE BACK AND SPINE WITH URGENT SURGICAL INDICATIONS 366 SCOLIOSIS 406 ENIGN CONDITIONS OF BONE AND JOINTS AT HIGH RISK FOR COMPLICATIONS 482 CLOSED DISLOCATIONS/FRACTURES OF NON-CERVICAL VERTEBRAL COLUMN WITHOUT NEUROLOGIC INJURY OR STRUCTURAL INSTABILITY 532 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS 561 BENIGN NEOPLASM OF BONE AND ARTICULAR CARTILAGE INCLUDING OSTEOID OSTEOMAS; BENIGN NEOPLASM OF CONNECTIVE AND OTHER SOFT TISSUE
22854	Insertion of intervertebral biomechanical device(s) (eg, synthetic cage, mesh) with integral anterior instrumentation for device anchoring (eg, screws, flanges), when performed, to vertebral corpectomy(ies) (vertebral body resection, partial or complete)	51, 154, 205, 259, 351, 366, 406, 482, 532, 561
22859	Insertion of intervertebral biomechanical device(s) (eg, synthetic cage, mesh, methylmethacrylate) to intervertebral disc space or vertebral body defect without interbody arthrodesis, each contiguous defect (List separately in addition to code for primary	51, 154, 205, 259, 351, 366, 406, 482, 532, 561

22867	Insertion of interlaminar/interspinous process stabilization/distraction device, without fusion, including image guidance when performed, with open decompression, lumbar; single level	Services recommended for non-coverage
22868	Insertion of interlaminar/interspinous process stabilization/distraction device, without fusion, including image guidance when performed, with open decompression, lumbar; second level (List separately in addition to code for primary procedure)	Services recommended for non-coverage
22869	Insertion of interlaminar/interspinous process stabilization/distraction device, without open decompression or fusion, including image guidance when performed, lumbar; single level	Services recommended for non-coverage
22870	Insertion of interlaminar/interspinous process stabilization/distraction device, without open decompression or fusion, including image guidance when performed, lumbar; second level (List separately in addition to code for primary procedure)	Services recommended for non-coverage
27197	Closed treatment of posterior pelvic ring fracture(s), dislocation(s), diastasis or subluxation of the ilium, sacroiliac joint, and/or sacrum, with or without anterior pelvic ring fracture(s) and/or dislocation(s) of the pubic symphysis and/or superior/inferior rami, unilateral or bilateral; without manipulation	187 FRACTURE OF PELVIS, OPEN AND CLOSED
27198	Closed treatment of posterior pelvic ring fracture(s), dislocation(s), diastasis or subluxation of the ilium, sacroiliac joint, and/or sacrum, with or without anterior pelvic ring fracture(s) and/or dislocation(s) of the pubic symphysis and/or superior/inferior rami, unilateral or bilateral; with manipulation, requiring more than local anesthesia (ie, general anesthesia, moderate sedation, spinal/epidural)	187 FRACTURE OF PELVIS, OPEN AND CLOSED
28291	Hallux rigidus correction with cheilectomy, debridement and capsular release of the first metatarsophalangeal joint; with implant	361 RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, OSTEOCHONDRITIS DISSECANS, AND ASEPTIC NECROSIS OF BONE

28295	Correction, hallux valgus (bunionectomy), with sesamoidectomy, when performed; with proximal metatarsal osteotomy, any method	545 DEFORMITIES OF FOOT
31551	Laryngoplasty; for laryngeal stenosis, with graft, without indwelling stent placement, younger than 12 years of age	47 CLEFT PALATE WITH AIRWAY OBSTRUCTION 70 LARYNGEAL STENOSIS OR PARALYSIS WITH AIRWAY COMPLICATIONS 521 PARALYSIS OF VOCAL CORDS OR LARYNX
31552	Laryngoplasty; for laryngeal stenosis, with graft, without indwelling stent placement, age 12 years or older	47, 70, 521
31553	Laryngoplasty; for laryngeal stenosis, with graft, with indwelling stent placement, younger than 12 years of age	47, 70, 521
31554	Laryngoplasty; for laryngeal stenosis, with graft, with indwelling stent placement, age 12 years or older	47, 70, 521
31572	Laryngoscopy, flexible; with ablation or destruction of lesion(s) with laser, unilateral	210 SUPERFICIAL ABSCESSES AND CELLULITIS 292 CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX 377 BENIGN NEOPLASM OF RESPIRATORY AND INTRATHORACIC ORGANS 641 BENIGN POLYPS OF VOCAL CORDS
31573	Laryngoscopy, flexible; with therapeutic injection(s) (eg, chemodenervation agent or corticosteroid, injected percutaneous, transoral, or via endoscope channel), unilateral	210 SUPERFICIAL ABSCESSES AND CELLULITIS 367 DYSTONIA (UNCONTROLLABLE); LARYNGEAL SPASM
31574	Laryngoscopy, flexible; with injection(s) for augmentation (eg, percutaneous, transoral), unilateral	70 LARYNGEAL STENOSIS OR PARALYSIS WITH AIRWAY COMPLICATIONS 521 PARALYSIS OF VOCAL CORDS OR LARYNX
31591	Laryngoplasty, medialization, unilateral	70 LARYNGEAL STENOSIS OR PARALYSIS WITH AIRWAY COMPLICATIONS 521 PARALYSIS OF VOCAL CORDS OR LARYNX
31592	Cricotracheal resection	267 CANCER OF LUNG, BRONCHUS, PLEURA, TRACHEA, MEDIASTINUM AND OTHER RESPIRATORY ORGANS 377 BENIGN NEOPLASM OF RESPIRATORY AND INTRATHORACIC ORGANS

33340	Percutaneous transcatheter closure of the left atrial appendage with endocardial implant, including fluoroscopy, transseptal puncture, catheter placement(s), left atrial angiography, left atrial appendage angiography, when performed, and radiological supe	Services recommended for non-coverage
33390	Valvuloplasty, aortic valve, open, with cardiopulmonary bypass; simple (ie, valvotomy, debridement, debulking, and/or simple commissural resuspension)	73 ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION 86 MYOCARDITIS, PERICARDITIS, AND ENDOCARDITIS 110 CONGENITAL STENOSIS AND INSUFFICIENCY OF AORTIC VALVE 190 RHEUMATIC MULTIPLE VALVULAR DISEASE 193 CHRONIC ISCHEMIC HEART DISEASE 228 DISEASES AND DISORDERS OF AORTIC VALVE 290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT
33391	Valvuloplasty, aortic valve, open, with cardiopulmonary bypass; complex (eg, leaflet extension, leaflet resection, leaflet reconstruction, or annuloplasty)	73 ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION 86 MYOCARDITIS, PERICARDITIS, AND ENDOCARDITIS 110 CONGENITAL STENOSIS AND INSUFFICIENCY OF AORTIC VALVE 190 RHEUMATIC MULTIPLE VALVULAR DISEASE 193 CHRONIC ISCHEMIC HEART DISEASE 228 DISEASES AND DISORDERS OF AORTIC VALVE 290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT
36456	Partial exchange transfusion, blood, plasma or crystalloid necessitating the skill of a physician or other qualified health care professional, newborn	Services recommended for non-coverage
36473	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, mechanochemical; first vein treated	384 CHRONIC ULCER OF SKIN 519 PHLEBITIS AND THROMBOPHLEBITIS, SUPERFICIAL 522 POSTTHROMBOTIC SYNDROME 643 VARICOSE VEINS OF LOWER EXTREMITIES WITHOUT ULCER OR OTHER MAJOR COMPLICATION

36474	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, mechanochemical; subsequent vein(s) treated in a single extremity, each through separate access sites (List separately in addition	384 CHRONIC ULCER OF SKIN 519 PHLEBITIS AND THROMBOPHLEBITIS, SUPERFICIAL 522 POSTTHROMBOTIC SYNDROME 643 VARICOSE VEINS OF LOWER EXTREMITIES WITHOUT ULCER OR OTHER MAJOR COMPLICATION
36901	Introduction of needle(s) and/or catheter(s), dialysis circuit, with diagnostic angiography of the dialysis circuit, including all direct puncture(s) and catheter placement(s), injection(s) of contrast, all necessary imaging from the arterial anastomosis and adjacent artery through entire venous outflow including the inferior or superior vena cava, fluoroscopic guidance, radiological supervision and interpretation and image documentation and report;	63 END STAGE RENAL DISEASE 131 ACUTE KIDNEY INJURY 226 DISORDERS OF FLUID, ELECTROLYTE, AND ACID-BASE BALANCE 290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 344 CHRONIC KIDNEY DISEASE
36902	Introduction of needle(s) and/or catheter(s), dialysis circuit, with diagnostic angiography of the dialysis circuit, including all direct puncture(s) and catheter placement(s), injection(s) of contrast, all necessary imaging from the arterial anastomosis and adjacent artery through entire venous outflow including the inferior or superior vena cava, fluoroscopic guidance, radiological supervision and interpretation and image documentation and report; with transluminal balloon angioplasty, peripheral dialysis segment, including all imaging and radiological supervision and interpretation necessary to perform the angioplasty	63 END STAGE RENAL DISEASE 131 ACUTE KIDNEY INJURY 226 DISORDERS OF FLUID, ELECTROLYTE, AND ACID-BASE BALANCE 290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 344 CHRONIC KIDNEY DISEASE

36903	Introduction of needle(s) and/or catheter(s), dialysis circuit, with diagnostic angiography of the dialysis circuit, including all direct puncture(s) and catheter placement(s), injection(s) of contrast, all necessary imaging from the arterial anastomosis and adjacent artery through entire venous outflow including the inferior or superior vena cava, fluoroscopic guidance, radiological supervision and interpretation and image documentation and report; with transcatheter placement of intravascular stent(s), peripheral dialysis segment, including all imaging and radiological supervision and interpretation necessary to perform the stenting, and all angioplasty within the peripheral dialysis segment	63 END STAGE RENAL DISEASE 131 ACUTE KIDNEY INJURY 226 DISORDERS OF FLUID, ELECTROLYTE, AND ACID-BASE BALANCE 290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 344 CHRONIC KIDNEY DISEASE
36904	Percutaneous transluminal mechanical thrombectomy and/or infusion for thrombolysis, dialysis circuit, any method, including all imaging and radiological supervision and interpretation, diagnostic angiography, fluoroscopic guidance, catheter placement(s), and intraprocedural pharmacological thrombolytic injection(s);	63 END STAGE RENAL DISEASE 131 ACUTE KIDNEY INJURY 226 DISORDERS OF FLUID, ELECTROLYTE, AND ACID-BASE BALANCE 290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 344 CHRONIC KIDNEY DISEASE
36905	Percutaneous transluminal mechanical thrombectomy and/or infusion for thrombolysis, dialysis circuit, any method, including all imaging and radiological supervision and interpretation, diagnostic angiography, fluoroscopic guidance, catheter placement(s), and intraprocedural pharmacological thrombolytic injection(s); with transluminal balloon angioplasty, peripheral dialysis segment, including all imaging and radiological supervision and interpretation necessary to perform the angioplasty	63 END STAGE RENAL DISEASE 131 ACUTE KIDNEY INJURY 226 DISORDERS OF FLUID, ELECTROLYTE, AND ACID-BASE BALANCE 290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 344 CHRONIC KIDNEY DISEASE

36906	Percutaneous transluminal mechanical thrombectomy and/or infusion for thrombolysis, dialysis circuit, any method, including all imaging and radiological supervision and interpretation, diagnostic angiography, fluoroscopic guidance, catheter placement(s), and intraprocedural pharmacological thrombolytic injection(s); with transcatheter placement of intravascular stent(s), peripheral dialysis segment, including all imaging and radiological supervision and interpretation necessary to perform the stenting, and all angioplasty within the peripheral dialysis circuit	63 END STAGE RENAL DISEASE 131 ACUTE KIDNEY INJURY 226 DISORDERS OF FLUID, ELECTROLYTE, AND ACID-BASE BALANCE 290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 344 CHRONIC KIDNEY DISEASE
36907	Transluminal balloon angioplasty, central dialysis segment, performed through dialysis circuit, including all imaging and radiological supervision and interpretation required to perform the angioplasty	63 END STAGE RENAL DISEASE 131 ACUTE KIDNEY INJURY 226 DISORDERS OF FLUID, ELECTROLYTE, AND ACID-BASE BALANCE 290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 344 CHRONIC KIDNEY DISEASE
36908	Transcatheter placement of intravascular stent(s), central dialysis segment, performed through dialysis circuit, including all imaging radiological supervision and interpretation required to perform the stenting, and all angioplasty in the central dialysis segment	63 END STAGE RENAL DISEASE 131 ACUTE KIDNEY INJURY 226 DISORDERS OF FLUID, ELECTROLYTE, AND ACID-BASE BALANCE 290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 344 CHRONIC KIDNEY DISEASE
36909	Dialysis circuit permanent vascular embolization or occlusion (including main circuit or any accessory veins), endovascular, including all imaging and radiological supervision and interpretation necessary to complete the intervention	63 END STAGE RENAL DISEASE 131 ACUTE KIDNEY INJURY 226 DISORDERS OF FLUID, ELECTROLYTE, AND ACID-BASE BALANCE 290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 344 CHRONIC KIDNEY DISEASE

37246	Transluminal balloon angioplasty (except lower extremity artery(ies) for occlusive disease, intracranial, coronary, pulmonary, or dialysis circuit), open or percutaneous, including all imaging and radiological supervision and interpretation necessary to perform the angioplasty within the same artery; initial artery	48 COARCTATION OF THE AORTA 74 CONGENITAL PULMONARY VALVE ANOMALIES 110 CONGENITAL STENOSIS AND INSUFFICIENCY OF AORTIC VALVE 228 DISEASES AND DISORDERS OF AORTIC VALVE 240 LIMB THREATENING VASCULAR DISEASE, INFECTIONS, AND VASCULAR COMPLICATIONS 290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 310 DISORDERS OF ARTERIES, OTHER THAN CAROTID OR CORONARY 354 NON-LIMB THREATENING PERIPHERAL VASCULAR DISEASE 452 ATHEROSCLEROSIS, AORTIC AND RENAL
37247	Transluminal balloon angioplasty (except lower extremity artery(ies) for occlusive disease, intracranial, coronary, pulmonary, or dialysis circuit), open or percutaneous, including all imaging and radiological supervision and interpretation necessary to perform the angioplasty within the same artery; each additional artery	48 COARCTATION OF THE AORTA 74 CONGENITAL PULMONARY VALVE ANOMALIES 110 CONGENITAL STENOSIS AND INSUFFICIENCY OF AORTIC VALVE 228 DISEASES AND DISORDERS OF AORTIC VALVE 240 LIMB THREATENING VASCULAR DISEASE, INFECTIONS, AND VASCULAR COMPLICATIONS 290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 310 DISORDERS OF ARTERIES, OTHER THAN CAROTID OR CORONARY 354 NON-LIMB THREATENING PERIPHERAL VASCULAR DISEASE 452 ATHEROSCLEROSIS, AORTIC AND RENAL
37248	Transluminal balloon angioplasty (except dialysis circuit), open or percutaneous, including all imaging and radiological supervision and interpretation necessary to perform the angioplasty within the same vein; initial vein	83 PHLEBITIS AND THROMBOPHLEBITIS, DEEP 240 LIMB THREATENING VASCULAR DISEASE, INFECTIONS, AND VASCULAR COMPLICATIONS 285 BUDD-CHIARI SYNDROME, AND OTHER VENOUS EMBOLISM AND THROMBOSIS 290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 354 NON-LIMB THREATENING PERIPHERAL VASCULAR DISEASE

37249	Transluminal balloon angioplasty (except dialysis circuit), open or percutaneous, including all imaging and radiological supervision and interpretation necessary to perform the angioplasty within the same vein; each additional vein (List separately in add	83 PHLEBITIS AND THROMBOPHLEBITIS, DEEP 240 LIMB THREATENING VASCULAR DISEASE, INFECTIONS, AND VASCULAR COMPLICATIONS 285 BUDD-CHIARI SYNDROME, AND OTHER VENOUS EMBOLISM AND THROMBOSIS 290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 354 NON-LIMB THREATENING PERIPHERAL VASCULAR DISEASE
43284	Laparoscopy, surgical, esophageal sphincter augmentation procedure, placement of sphincter augmentation device (ie, magnetic band), including cruroplasty when performed	Services recommended for non-coverage
43285	Removal of esophageal sphincter augmentation device	428 COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT
58674	Laparoscopy, surgical, ablation of uterine fibroid(s) including intraoperative ultrasound guidance and monitoring, radiofrequency	Services recommended for non-coverage
62320	Injection(s), of diagnostic or therapeutic substance(s) (eg, anesthetic, antispasmodic, opioid, steroid, other solution), not including neurolytic substances, including needle or catheter placement, interlaminar epidural or subarachnoid, cervical or thoracic; without imaging guidance	75 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES 297 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS
62321	Injection(s), of diagnostic or therapeutic substance(s) (eg, anesthetic, antispasmodic, opioid, steroid, other solution), not including neurolytic substances, including needle or catheter placement, interlaminar epidural or subarachnoid, cervical or thoracic, with imaging guidance (ie, fluoroscopy or CT)	75 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES 297 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS
62322	Injection(s), of diagnostic or therapeutic substance(s) (eg, anesthetic, antispasmodic, opioid, steroid, other solution), not including neurolytic substances, including needle or catheter placement, interlaminar epidural or subarachnoid, lumbar or sacral (caudal); without imaging guidance	75 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES 297 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS

62323	Injection(s), of diagnostic or therapeutic substance(s) (eg, anesthetic, antispasmodic, opioid, steroid, other solution), not including neurolytic substances, including needle or catheter placement, interlaminar epidural or subarachnoid, lumbar or sacral (caudal); with imaging guidance (ie, fluoroscopy or CT)	75 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES 297 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS
62324	Injection(s), including indwelling catheter placement, continuous infusion or intermittent bolus, of diagnostic or therapeutic substance(s) (eg, anesthetic, antispasmodic, opioid, steroid, other solution), not including neurolytic substances, interlaminar epidural or subarachnoid, cervical or thoracic; without imaging guidance	Ancillary
62325	Injection(s), including indwelling catheter placement, continuous infusion or intermittent bolus, of diagnostic or therapeutic substance(s) (eg, anesthetic, antispasmodic, opioid, steroid, other solution), not including neurolytic substances, interlaminar epidural or subarachnoid, cervical or thoracic; with imaging guidance (ie, fluoroscopy or CT)	Ancillary
62326	Injection(s), including indwelling catheter placement, continuous infusion or intermittent bolus, of diagnostic or therapeutic substance(s) (eg, anesthetic, antispasmodic, opioid, steroid, other solution), not including neurolytic substances, interlaminar epidural or subarachnoid, lumbar or sacral (caudal); without imaging guidance	Ancillary
62327	Injection(s), including indwelling catheter placement, continuous infusion or intermittent bolus, of diagnostic or therapeutic substance(s) (eg, anesthetic, antispasmodic, opioid, steroid, other solution), not including neurolytic substances, interlaminar epidural or subarachnoid, lumbar or sacral (caudal); with imaging guidance (ie, fluoroscopy or CT)	Ancillary
62380	Endoscopic decompression of spinal cord, nerve root(s), including laminotomy, partial facetectomy, foraminotomy, discectomy and/or excision of herniated intervertebral disc, 1 interspace, lumbar	Services recommended for non-coverage

76706	Ultrasound, abdominal aorta, real time with image documentation, screening study for abdominal aortic aneurysm (AAA)	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS 625 PREVENTION SERVICES WITH LIMITED OR NO EVIDENCE OF EFFECTIVENESS
77065	Diagnostic mammography, including computer-aided detection (CAD) when performed; unilateral	Diagnostic Procedures File
77066	Diagnostic mammography, including computer-aided detection (CAD) when performed; bilateral	Diagnostic Procedures File
77067	Screening mammography, bilateral (2-view study of each breast), including computer-aided detection (CAD) when performed	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
80305	Drug test(s), presumptive, any number of drug classes, any number of devices or procedures (eg, immunoassay); capable of being read by direct optical observation only (eg, dipsticks, cups, cards, cartridges) includes sample validation when performed, per	Diagnostic Procedures File
80306	Drug test(s), presumptive, any number of drug classes, any number of devices or procedures (eg, immunoassay); read by instrument assisted direct optical observation (eg, dipsticks, cups, cards, cartridges), includes sample validation when performed, per d	Diagnostic Procedures File
80307	Drug test(s), presumptive, any number of drug classes, any number of devices or procedures, by instrument chemistry analyzers (eg, utilizing immunoassay [eg, EIA, ELISA, EMIT, FPIA, IA, KIMS, RIA]), chromatography (eg, GC, HPLC), and mass spectrometry eit	Diagnostic Procedures File
81327	SEPT9 (Septin9) (eg, colorectal cancer) methylation analysis	Services recommended for non-coverage
81413	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence analysis panel, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCN	Diagnostic Workup File

81414	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); duplication/deletion gene analysis panel, must include analysis of at least 2 genes, including KCNH2 and KCNQ1	Diagnostic Workup File
81422	Fetal chromosomal microdeletion(s) genomic sequence analysis (eg, DiGeorge syndrome, Cri-du-chat syndrome), circulating cell-free fetal DNA in maternal blood	Services recommended for non-coverage
81439	Inherited cardiomyopathy (eg, hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy) genomic sequence analysis panel, must include sequencing of at least 5 genes, including DSG2, MYBPC3, MYH7, PKP2, and TTN	Diagnostic Workup File
81539	Oncology (high-grade prostate cancer), biochemical assay of four proteins (Total PSA, Free PSA, Intact PSA, and human kallikrein-2 [hK2]), utilizing plasma or serum, prognostic algorithm reported as a probability score	Services recommended for non-coverage
84410	Testosterone; bioavailable, direct measurement (eg, differential precipitation)	Diagnostic Procedures File
87483	Infectious agent detection by nucleic acid (DNA or RNA); central nervous system pathogen (eg, Neisseria meningitidis, Streptococcus pneumoniae, Listeria, Haemophilus influenzae, E. coli, Streptococcus agalactiae, enterovirus, human parechovirus, herpes si	Diagnostic Procedures File
90674	Influenza virus vaccine, quadrivalent (ccIIV4), derived from cell cultures, subunit, preservative and antibiotic free, 0.5 mL dosage, for intramuscular use	Line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
90697	Diphtheria, tetanus toxoids, acellular pertussis vaccine, inactivated poliovirus vaccine, Haemophilus influenzae type b PRP-OMP conjugate vaccine, and hepatitis B vaccine (DTaP-IPV-Hib-HepB), for intramuscular use	Line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS

92242	Fluorescein angiography and indocyanine-green angiography (includes multiframe imaging) performed at the same patient encounter with interpretation and report, unilateral or bilateral	100,117,143,159,171, 175, 179, 248, 249, 252, 270, 274, 278,284,301, 302, 304, 313, 315, 323, 324, 340, 341, 342, 353, 356, 359, 365, 370, 372, 375, 379, 388, 399, 410, 441, 445, 453, 455, 456, 464, 475, 476, 488, 499, 505, 564, 567, 572, 597, 630, 636, 644
93590	Percutaneous transcatheter closure of paravalvular leak; initial occlusion device, mitral valve	290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT
93591	Percutaneous transcatheter closure of paravalvular leak; initial occlusion device, aortic valve	290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT
93592	Percutaneous transcatheter closure of paravalvular leak; each additional occlusion device (List separately in addition to code for primary procedure)	290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT
96160	Administration of patient-focused health risk assessment instrument (eg, health hazard appraisal) with scoring and documentation, per standardized instrument	Diagnostic Procedures File
96161	Administration of caregiver-focused health risk assessment instrument (eg, depression inventory) for the benefit of the patient, with scoring and documentation, per standardized instrument	Diagnostic Procedures File
96377	Application of on-body injector (includes cannula insertion) for timed subcutaneous injection	All lines with chemotherapy
96936	Reflectance confocal microscopy (RCM) for cellular and sub-cellular imaging of skin; interpretation and report only, each additional lesion (List separately in addition to code for primary procedure)	Services recommended for non-coverage
97161	Physical therapy evaluation: low complexity, requiring these components: A history with no personal factors and/or comorbidities that impact the plan of care; An examination of body system(s) using standardized tests and measures addressing 1-2 elements f	All lines with 97001 currently 34,50,61,72,75,76,78,85,95, 96,135, 136, 140, 154, 157, 164, 182, 187, 188, 200, 201, 205, 206, 212, 259, 261, 276, 290, 297, 306, 314, 317, 322, 346, 350, 351, 353, 360, 361, 364, 366, 381, 382, 392, 406, 407, 413, 421, 423, 427, 428, 436, 447, 459, 467, 470, 471, 482, 490, 512, 532, 558, 561, 574, 592, 611

97162	Physical therapy evaluation: moderate complexity, requiring these components: A history of present problem with 1-2 personal factors and/or comorbidities that impact the plan of care; An examination of body systems using standardized tests and measures in	All lines with 97001 currently
97163	Physical therapy evaluation: high complexity, requiring these components: A history of present problem with 3 or more personal factors and/or comorbidities that impact the plan of care; An examination of body systems using standardized tests and measures	All lines with 97001 currently
97164	Re-evaluation of physical therapy established plan of care, requiring these components: An examination including a review of history and use of standardized tests and measures is required; and Revised plan of care using a standardized patient assessment i	All lines with 97001 currently
97165	Occupational therapy evaluation, low complexity, requiring these components: An occupational profile and medical and therapy history, which includes a brief history including review of medical and/or therapy records relating to the presenting problem; An	All lines with 97003 currently 34,50,61,72,75,76,78,85,95,96, 135, 136, 140, 154, 157, 164, 182, 187, 188, 200, 201, 205, 206, 212, 259, 261, 276, 290, 297, 306, 314, 322, 346, 350, 351, 353, 360, 361, 364, 366, 381, 382, 392, 406, 407, 413, 421, 423, 427, 428, 436, 447, 467, 471, 482, 490, 512, 532, 558, 561, 574, 592, 611
97166	Occupational therapy evaluation, moderate complexity, requiring these components: An occupational profile and medical and therapy history, which includes an expanded review of medical and/or therapy records and additional review of physical, cognitive, or	All lines with 97003 currently
97167	Occupational therapy evaluation, high complexity, requiring these components: An occupational profile and medical and therapy history, which includes review of medical and/or therapy records and extensive additional review of physical, cognitive, or psych	All lines with 97003 currently

97168	Re-evaluation of occupational therapy established plan of care, requiring these components: An assessment of changes in patient functional or medical status with revised plan of care; An update to the initial occupational profile to reflect changes in con	All lines with 97003 currently
97169	Athletic training evaluation, low complexity, requiring these components: A history and physical activity profile with no comorbidities that affect physical activity; An examination of affected body area and other symptomatic or related systems addressing	Services recommended for non-coverage
97170	Athletic training evaluation, moderate complexity, requiring these components: A medical history and physical activity profile with 1-2 comorbidities that affect physical activity; An examination of affected body area and other symptomatic or related syst	Services recommended for non-coverage
97171	Athletic training evaluation, high complexity, requiring these components: A medical history and physical activity profile, with 3 or more comorbidities that affect physical activity; A comprehensive examination of body systems using standardized tests an	Services recommended for non-coverage
97172	Re-evaluation of athletic training established plan of care requiring these components: An assessment of patient's current functional status when there is a documented change; and A revised plan of care using a standardized patient assessment instrument a	Services recommended for non-coverage
99151	Moderate sedation services provided by the same physician or other qualified health care professional performing the diagnostic or therapeutic service that the sedation supports, requiring the presence of an independent trained observer to assist in the m	Ancillary

99152	Moderate sedation services provided by the same physician or other qualified health care professional performing the diagnostic or therapeutic service that the sedation supports, requiring the presence of an independent trained observer to assist in the m	Ancillary
99153	Moderate sedation services provided by the same physician or other qualified health care professional performing the diagnostic or therapeutic service that the sedation supports, requiring the presence of an independent trained observer to assist in the m	Ancillary
99155	Moderate sedation services provided by a physician or other qualified health care professional other than the physician or other qualified health care professional performing the diagnostic or therapeutic service that the sedation supports; initial 15 min	Ancillary
99156	Moderate sedation services provided by a physician or other qualified health care professional other than the physician or other qualified health care professional performing the diagnostic or therapeutic service that the sedation supports; initial 15 min	Ancillary
99157	Moderate sedation services provided by a physician or other qualified health care professional other than the physician or other qualified health care professional performing the diagnostic or therapeutic service that the sedation supports; each additiona	Ancillary

Code	DESCRIPTION	Placement
G0490	Face-to-face home health nursing visit by a rural health clinic (rhc) or federally qualified health center (fqhc) in an area with a shortage of home health agencies; (services limited to rn or lpn only)	Any line with 99374 and 99375 (Supervision of a patient under care of home health agency)
G0493	Skilled services of a registered nurse (rn) for the observation and assessment of the patient's condition, each 15 minutes (the change in the patient's condition requires skilled nursing personnel to identify and evaluate the patient's need for possible modification of treatment in the home health or hospice setting)	Ancillary
G0494	Skilled services of a licensed practical nurse (lpn) for the observation and assessment of the patient's condition, each 15 minutes (the change in the patient's condition requires skilled nursing personnel to identify and evaluate the patient's need for possible modification of treatment in the home health or hospice setting)	Ancillary
G0495	Skilled services of a registered nurse (rn), in the training and/or education of a patient or family member, in the home health or hospice setting, each 15 minutes	Ancillary
G0496	Skilled services of a licensed practical nurse (lpn), in the training and/or education of a patient or family member, in the home health or hospice setting, each 15 minutes	Ancillary
G0500	Moderate sedation services provided by the same physician or other qualified health care professional performing a gastrointestinal endoscopic service that sedation supports, requiring the presence of an independent trained observer to assist in the monitoring of the patient's level of consciousness and physiological status; initial 15 minutes of intra-service time; patient age 5 years or older (additional time may be reported with 99153, as appropriate)	Ancillary
G0501	Resource-intensive services for patients for whom the use of specialized mobility-assistive technology (such as adjustable height chairs or tables, patient lift, and adjustable padded leg supports) is medically necessary and used during the provision of an office/outpatient, evaluation and management visit (list separately in addition to primary service)	Ancillary
G0502	Initial psychiatric collaborative care management, first 70 minutes in the first calendar month of behavioral health care manager activities, in consultation with a psychiatric consultant, and directed by the treating physician or other qualified health care professional, with the following required elements: outreach to and engagement in treatment of a patient directed by the treating physician or other qualified health care professional; initial assessment of the patient, including administration of validated rating scales, with the development of an individualized treatment plan; review by the psychiatric consultant with modifications of the plan if recommended; entering patient in a registry and tracking patient follow-up and progress using the registry, with appropriate documentation, and participation in weekly caseload consultation with the psychiatric consultant; and provision of brief interventions using evidence-based techniques such as behavioral activation, motivational interviewing, and other focused treatment strategies	Ancillary

G0503	Subsequent psychiatric collaborative care management, first 60 minutes in a subsequent month of behavioral health care manager activities, in consultation with a psychiatric consultant, and directed by the treating physician or other qualified health care professional, with the following required elements: tracking patient follow-up and progress using the registry, with appropriate documentation; participation in weekly caseload consultation with the psychiatric consultant; ongoing collaboration with and coordination of the patient's mental health care with the treating physician or other qualified health care professional and any other treating mental health providers; additional review of progress and recommendations for changes in treatment, as indicated, including medications, based on recommendations provided by the psychiatric consultant; provision of brief interventions using evidence-based techniques such as behavioral activation, motivational interviewing, and other focused treatment strategies; monitoring of patient outcomes using validated rating scales; and relapse prevention planning with patients as they achieve remission of symptoms and/or other treatment goals and are prepared for discharge from active treatment	Ancillary
G0504	Initial or subsequent psychiatric collaborative care management, each additional 30 minutes in a calendar month of behavioral health care manager activities, in consultation with a psychiatric consultant, and directed by the treating physician or other qualified health care professional (list separately in addition to code for primary procedure); (use g0504 in conjunction with g0502, g0503)	Ancillary
G0505	Cognition and functional assessment using standardized instruments with development of recorded care plan for the patient with cognitive impairment, history obtained from patient and/or caregiver, in office or other outpatient setting or home or domiciliary or rest home	Diagnostic Procedures File
G0506	Comprehensive assessment of and care planning for patients requiring chronic care management services (list separately in addition to primary monthly care management service)	Ancillary
G0507	Care management services for behavioral health conditions, at least 20 minutes of clinical staff time, directed by a physician or other qualified health care professional, per calendar month, with the following required elements: initial assessment or follow-up monitoring, including the use of applicable validated rating scales; behavioral health care planning in relation to behavioral/psychiatric health problems, including revision for patients who are not progressing or whose status changes; facilitating and coordinating treatment such as psychotherapy, pharmacotherapy, counseling and/or psychiatric consultation; and continuity of care with a designated member of the care team	Ancillary
G0508	Telehealth consultation, critical care, initial , physicians typically spend 60 minutes communicating with the patient and providers via telehealth	Inpatient lines on Prioritized List
G0509	Telehealth consultation, critical care, subsequent, physicians typically spend 50 minutes communicating with the patient and providers via telehealth	Inpatient lines on Prioritized List

G9481	Remote in-home visit for the evaluation and management of a new patient for use only in the medicare-approved comprehensive care for joint replacement model, which requires these 3 key components: a problem focused history; a problem focused examination; and straightforward medical decision making, furnished in real time using interactive audio and video technology. counseling and coordination of care with other physicians, other qualified health care professionals or agencies are provided consistent with the nature of the problem(s) and the needs of the patient or the family or both. usually, the presenting problem(s) are self limited or minor. typically, 10 minutes are spent with the patient or family or both via real time, audio and video intercommunications technology	Ancillary
G9482	Remote in-home visit for the evaluation and management of a new patient for use only in the medicare-approved comprehensive care for joint replacement model, which requires these 3 key components: an expanded problem focused history; an expanded problem focused examination; straightforward medical decision making, furnished in real time using interactive audio and video technology. counseling and coordination of care with other physicians, other qualified health care professionals or agencies are provided consistent with the nature of the problem(s) and the needs of the patient or the family or both. usually, the presenting problem(s) are of low to moderate severity. typically, 20 minutes are spent with the patient or family or both via real time, audio and video intercommunications technology	Ancillary
G9483	Remote in-home visit for the evaluation and management of a new patient for use only in the medicare-approved comprehensive care for joint replacement model, which requires these 3 key components: a detailed history; a detailed examination; medical decision making of low complexity, furnished in real time using interactive audio and video technology. counseling and coordination of care with other physicians, other qualified health care professionals or agencies are provided consistent with the nature of the problem(s) and the needs of the patient or the family or both. usually, the presenting problem(s) are of moderate severity. typically, 30 minutes are spent with the patient or family or both via real time, audio and video intercommunications technology	Ancillary
G9484	Remote in-home visit for the evaluation and management of a new patient for use only in the medicare-approved comprehensive care for joint replacement model, which requires these 3 key components: a comprehensive history; a comprehensive examination; medical decision making of moderate complexity, furnished in real time using interactive audio and video technology. counseling and coordination of care with other physicians, other qualified health care professionals or agencies are provided consistent with the nature of the problem(s) and the needs of the patient or the family or both. usually, the presenting problem(s) are of moderate to high severity. typically, 45 minutes are spent with the patient or family or both via real time, audio and video intercommunications technology	Ancillary

G9485	Remote in-home visit for the evaluation and management of a new patient for use only in the medicare-approved comprehensive care for joint replacement model, which requires these 3 key components: a comprehensive history; a comprehensive examination; medical decision making of high complexity, furnished in real time using interactive audio and video technology. counseling and coordination of care with other physicians, other qualified health care professionals or agencies are provided consistent with the nature of the problem(s) and the needs of the patient or the family or both. usually, the presenting problem(s) are of moderate to high severity. typically, 60 minutes are spent with the patient or family or both via real time, audio and video intercommunications technology	Ancillary
G9486	Remote in-home visit for the evaluation and management of an established patient for use only in the medicare-approved comprehensive care for joint replacement model, which requires at least 2 of the following 3 key components: a problem focused history; a problem focused examination; straightforward medical decision making, furnished in real time using interactive audio and video technology. counseling and coordination of care with other physicians, other qualified health care professionals or agencies are provided consistent with the nature of the problem(s) and the needs of the patient or the family or both. usually, the presenting problem(s) are self limited or minor. typically, 10 minutes are spent with the patient or family or both via real time, audio and video intercommunications technology	Ancillary
G9487	Remote in-home visit for the evaluation and management of an established patient for use only in the medicare-approved comprehensive care for joint replacement model, which requires at least 2 of the following 3 key components: an expanded problem focused history; an expanded problem focused examination; medical decision making of low complexity, furnished in real time using interactive audio and video technology. counseling and coordination of care with other physicians, other qualified health care professionals or agencies are provided consistent with the nature of the problem(s) and the needs of the patient or the family or both. usually, the presenting problem(s) are of low to moderate severity. typically, 15 minutes are spent with the patient or family or both via real time, audio and video intercommunications technology	Ancillary
G9488	Remote in-home visit for the evaluation and management of an established patient for use only in the medicare-approved comprehensive care for joint replacement model, which requires at least 2 of the following 3 key components: a detailed history; a detailed examination; medical decision making of moderate complexity, furnished in real time using interactive audio and video technology. counseling and coordination of care with other physicians, other qualified health care professionals or agencies are provided consistent with the nature of the problem(s) and the needs of the patient or the family or both. usually, the presenting problem(s) are of moderate to high severity. typically, 25 minutes are spent with the patient or family or both via real time, audio and video intercommunications technology	Ancillary

G9489	Remote in-home visit for the evaluation and management of an established patient for use only in the medicare-approved comprehensive care for joint replacement model, which requires at least 2 of the following 3 key components: a comprehensive history; a comprehensive examination; medical decision making of high complexity, furnished in real time using interactive audio and video technology. counseling and coordination of care with other physicians, other qualified health care professionals or agencies are provided consistent with the nature of the problem(s) and the needs of the patient or the family or both. usually, the presenting problem(s) are of moderate to high severity. typically, 40 minutes are spent with the patient or family or both via real time, audio and video intercommunications technology	Ancillary
G9490	Comprehensive care for joint replacement model, home visit for patient assessment performed by clinical staff for an individual not considered homebound, including, but not necessarily limited to patient assessment of clinical status, safety/fall prevention, functional status/ambulation, medication reconciliation/management, compliance with orders/plan of care, performance of activities of daily living, and ensuring beneficiary connections to community and other services. (for use only in the medicare-approved cjr model); may not be billed for a 30 day period covered by a transitional care management code	Ancillary
G9678	Oncology care model (ocm) monthly enhanced oncology services (meos) payment for ocm enhanced services. g9678 payments may only be made to ocm practitioners for ocm beneficiaries for the furnishment of enhanced services as defined in the ocm participation agreement	Ancillary
G9686	Onsite nursing facility conference, that is separate and distinct from an evaluation and management visit, including qualified practitioner and at least one member of the nursing facility interdisciplinary care team	Ancillary
G9770	Peripheral nerve block (pnb)	Informational
S0285	Colonoscopy consultation performed prior to a screening colonoscopy procedure	3 PREVENTIVE SERVICES
S0311	Comprehensive management and care coordination for advanced illness, per calendar month	Ancillary
T1040	Medicaid certified community behavioral health clinic services, per diem	Ancillary
T1041	Medicaid certified community behavioral health clinic services, per month	Ancillary

Appendix C
NEW GUIDELINES

GUIDELINE NOTE XXX PERCUTANEOUS REPAIR OF PARAVALVULAR LEAKS
Line 290
Percutaneous transcatheter closure of paravalvular leak (CPT 93590-93592) is included on this line only for patients with

1) prosthetic heart valves with paravalvular leak AND
2) intractable hemolysis or NYHA class III/IV heart failure AND
3) who are at high risk for surgery and have anatomic features suitable for catheter-based therapy AND
4) when performed in centers with expertise in the procedure.

GUIDELINE NOTE XXX DIAGNOSTIC TESTING FOR LIVER FIBROSIS TO GUIDE TREATMENT OF HEPATITIS C IN NON-CIRRHOTIC PATIENTS
Line 203

If a fibrosis score of ≥F2 is the threshold for antiviral treatment of Hepatitis C, the following are included on this line:

Imaging tests:

- Transient elastography (FibroScan®)
- Acoustic radiation force impulse imaging (ARFI) (Virtual Touch™ tissue quantification, ElastPQ)
- Shear wave elastography (SWE) (Aixplorer®)

Blood tests (only if imaging tests are unavailable):

- Enhanced Liver Fibrosis (ELF™)
- Fibrometer™
- FIBROSpect® II

If a fibrosis score of ≥F3 is the threshold for antiviral treatment of Hepatitis C, one or more of the following are included on this line:

Imaging tests:

- Transient elastography (FibroScan®)
- Acoustic radiation force impulse imaging (ARFI)
- Shear wave elastography (SWE)

Magnetic resonance elastography is included on this line for ≥F2 or ≥F3 only when at least one imaging test (FibroScan, ARFI, and SWE) has resulted in indeterminant results, a second one is similarly indeterminant, contraindicated or unavailable, and MRE is readily available.

Noninvasive tests are covered no more often than once per year.

The following tests are not included on this line (or any other line):

- Real time tissue elastography

Appendix C
NEW GUIDELINES

- Hepascore® (FibroScore®)
- FibroSure® (FibroTest®)

The development of this guideline note was informed by a HERC Coverage Guidance. See http://www.oregon.gov/oha/herc/Pages/blog-liver-fibrosis.diagnosis.aspx

GUIDELINE XXX, SACROILIAC JOINT FUSION

Line 532

Sacroiliac (SI) joint fusion (CPT 27279) is included on this line for patients who have all of the following:

1. Baseline score of at least 30% on the Oswestry Disability Index (ODI)
2. Undergone and failed a minimum six months of intensive non-operative treatment that must include non-opioid medication optimization and active therapy. Active therapy is defined as activity modification, chiropractic/osteopathic manipulative therapy, bracing, and/or active therapeutic exercise targeted at the lumbar spine, pelvis, SI joint and hip including a home exercise program. Failure of conservative therapy is defined as less than a 50% improvement on the ODI.
3. Typically unilateral pain that is caudal to the lumbar spine (L5 vertebrae), localized over the posterior SI joint, and consistent with SI joint pain.
4. Thorough physical examination demonstrating localized tenderness with palpation over the sacral sulcus (Fortin's point, i.e. at the insertion of the long dorsal ligament inferior to the posterior superior iliac spine) in the absence of tenderness of similar severity elsewhere (e.g. greater trochanter, lumbar spine, coccyx) and that other obvious sources for their pain do not exist.
5. Positive response to at least three of six provocative tests (e.g. thigh thrust test, compression test, Gaenslen's test, distraction test, Patrick's sign, posterior provocation test).
6. Absence of generalized pain behavior (e.g. somatoform disorder) and generalized pain disorders (e.g. fibromyalgia).
7. Diagnostic imaging studies that include ALL of the following:
    a. Imaging (plain radiographs and a CT or MRI) of the SI joint that excludes the presence of destructive lesions (e.g. tumor, infection), fracture, traumatic SI joint instability, or inflammatory arthropathy that would not be properly addressed by percutaneous SIJ fusion
    b. Imaging of the pelvis (AP plain radiograph) to rule out concomitant hip pathology
    c. Imaging of the lumbar spine (CT or MRI) to rule out neural compression or other degenerative condition that can be causing low back or buttock pain
    d. Imaging of the SI joint that indicates evidence of injury and/or degeneration
    e.

At least 75 percent reduction of pain for the expected duration of two anesthetics (on separate visits each with a different duration of action), and the ability to perform previously painful maneuvers, following an image-guided, contrast-enhanced intra-articular SI joint injection.SI

joint injections (CPT 20610 and 27096) are included on this line for diagnostic SI joint injections with anesthetic only, but not for therapeutic injections or corticosteroid injections. Injections are only included on this line for patients for whom SI joint fusion surgery is being considered.

Note: initially approved as a diagnostic guideline, but converted to a guideline attached to line 532 and merged with the other approved SI joint fusion guideline as discussed in the minutes above. *Minor wording changes were made to the approved guideline wording to allow these changes*

GUIDELINE NOTE XXX SKIN SUBSTITUTES FOR CHRONIC SKIN ULCERS
Line 384

Skin substitutes for chronic venous leg ulcers and chronic diabetic foot ulcers are included on this line when all of the following criteria are met:

1) FDA indications and contraindications are followed, if applicable
2) Wound has adequate arterial flow (ABI > 0.7), no ongoing infection and a moist wound healing environment
3) For patients with diabetes, Hba1c level is < 12
4) Prior appropriate wound care therapy (including but not limited to appropriate offloading, multilayer compression dressings and smoking cessation counseling) has failed to result in significant improvement (defined as at least a 50 percent reduction in ulcer surface area) of the wound over at least 30 days
5) Ongoing coverage requires significant improvement of the ulcer with skin substitute application over the preceding 6 week time period
6) Patients is able to adhere to the treatment plan
7) The use of skin substitutes is not included on this line for chronic skin ulcers other than venous leg ulcers and diabetic foot ulcers (e.g., pressure ulcers)

Note: There is no evidence supporting superiority of one skin substitute versus another and new studies are constantly being published. Decisions for specific products could be made based on at least one supportive randomized controlled trial, and those that involve fewer applications, and are lower cost.

MULTISECTOR INTERVENTIONS: PREVENTION AND TREATMENT OF OBESITY
Limited evidence supports the following interventions:

School and childcare settings

- School based interventions to reduce BMI (especially with physical activity focus)
- School nutrition policy and day care meal standards
- Family-based group education programs delivered in schools
- Obesity prevention interventions in childcare settings (nutrition education, healthy cooking classes for 2-6 year olds, physical activity and playful games)

Appendix C
NEW GUIDELINES

Community level interventions

- Environmental interventions (social marketing, cafeteria signs, farmers markets, walking groups, etc)
- Introduction of light rail
- Community-based group health education and counseling interventions, workplace education interventions
- Workplace and college interventions to improve physical activity

Multiple settings:

- Interventions to reduce sedentary screen time (in some studies, also to increase physical activity and nutrition).
- Multicomponent individual mentored health promotion programs to prevent childhood obesity
- Parental support interventions for diet and physical activity (group education, mental health counseling)

Policy changes

- Sugar sweetened beverage taxes
- Elimination of tax subsidy for advertising unhealthy food to children

This Multisector Interventions statement is based on the work of the HERC Obesity Task Force and the full summary of the evidence report is available here: http://www.oregon.gov/oha/herc/Pages/blog-obesityMSI.aspx

GUIDELINE NOTE XXX LONG-ACTING REVERSIBLE CONTRACEPTIVE (LARC) PLACEMENT

Line 6

Long-acting reversible contraceptives (implant or intrauterine device) are included on Line 6 in all settings, including (but not limited to) immediately postpartum and postabortion.

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/herc/Pages/blog-long-acting-reversible-contraceptives.aspx. HERC leadership added a letter (http://www.oregon.gov/oha/herc/Documents/LARC-Implementation.pdf) to Medical Directors regarding implementation issues, which references CMS requirements around contraceptive coverage and guidance on ways to implement effective LARC policy.

Appendix D
DELETED GUIDELINE NOTES

~~GUIDELINE NOTE 76, LIVER ELASTOGRAPHY~~
~~Line 203~~
~~Liver elastography (CPT 91200) is included on this line only when the non-invasive test would replace liver biopsy for determination of eligibility for medications for chronic hepatitis C. Performance of liver elastography more than twice per year or within six months following a liver biopsy is not included on this line.~~

Section 2.0

Staff Report

Errata
February 2017

1) CPT 19357-19380 (Breast reconstruction) are not included in the gender dysphoria line but these codes appear in the gender dysphoria guideline. The intent was not to include these codes for gender dysphoria as they are used for post-mastectomy reconstruction and not appropriate for this line. The CPT codes were removed from the gender dysphoria guideline
    a. Relevant excerpt from GN127
        i. 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 any contraindication to, intolerance of or patient refusal of hormonal therapy.
2) Add CPT 64905 (Nerve pedicle transfer; first stage) to line 70 LARYNGEAL STENOSIS OR PARALYSIS WITH AIRWAY COMPLICATIONS
    a. This code is the correct CPT code for laryngeal re-innervation, which was added as a covered benefit effective October 1, 2016.
3) The negative pressure wound therapy guideline contains 2 HCPCS codes that are no longer valid and were removed.

    GUIDELINE NOTE 62, NEGATIVE PRESSURE WOUND THERAPY

    Lines 8,30,51,84,210,212,240,290,384,428

    Negative pressure wound therapy (CPT 97605-97608~~, HCPCS G0456, G0457~~) is included on these lines only for patients who:

    - Have wounds that are refractory to or have failed standard therapies;
    - Are not suitable candidates for surgical wound closure; or,
    - Are at high risk for delayed or non-healing wounds due to factors such as compromised blood flow, diabetic complications, wounds with high risk of fecal contamination, extremely exudative wounds, and similar situations.

Section 3.0

OHAP report

OHAP Prioritized List Changes for HERC Approval
January 2017

1) Interim Prioritized List changes
    a. Add K02 series (Dental caries) to line 349 DENTAL CONDITIONS (EG. SEVERE CARIES, INFECTION) Treatment: ORAL SURGERY (I.E. EXTRACTIONS AND OTHER INTRAORAL SURGICAL PROCEDURES)
    b. Add D7210 (SURGICAL REMOVAL OF ERUPTED TOOTH REQUIRING REMOVAL OF BONE AND/OR SECTIONING OF TOOTH, AND INCLUDING ELEVATION OF MUCOPERIOSTEAL FLAP IF INDICATED) to line 349
    c. Modify GN34 as shown below:

GUIDELINE NOTE 34, ~~ORAL SURGERY~~ EXTRACTION OF IMPACTED WISDOM TEETH

Line 349

~~Treatment only for symptomatic dental pain, infection, bleeding or swelling (D7220, D7230, D7240, D7241, D7250).~~

Extraction of impacted wisdom teeth (D7220, D7230, D7240, D7241, D7250) is only included on this line when there is

1) evidence of pathology. Such pathology includes unrestorable caries, non-treatable pulpal and/or periapical pathology, cellulitis, abscess and osteomyelitis, internal/external resorption of the tooth or adjacent teeth, fracture of tooth, disease of follicle including cyst/tumour, tooth/teeth impeding surgery or reconstructive jaw surgery, and when a tooth is involved in or within the field of tumour resection OR
2) two or more episodes of pericoronitis OR
3) severe pain directly related to the impacted tooth that does not respond to conservative treatment
    a. extraction for pain or discomfort related to normal tooth eruption or for non-specific symptoms such as “headaches” or “jaw pain” is not considered medically or dentally necessary for treatment.

2) 2018 Biennial review
    a. Add CDT D6100 (IMPLANT REMOVAL, BY REPORT) to line 349 DENTAL CONDITIONS (EG. SEVERE CARIES, INFECTION) Treatment: ORAL SURGERY (I.E. EXTRACTIONS AND OTHER INTRAORAL SURGICAL PROCEDURES)
    b. Add D5221-D5222 (Immediate partial denture – resin base) to line 457 DENTAL CONDITIONS (EG. MISSING TEETH, PROSTHESIS FAILURE) Treatment: REMOVABLE PROSTHODONTICS (E.G. FULL AND PARTIAL DENTURES, RELINES) and removed from line 594 DENTAL CONDITIONS (EG. CARIES, FRACTURED TOOTH) Treatment: ADVANCED RESTORATIVE-ELECTIVE (INLAYS, ONLAYS, GOLD FOIL AND HIGH NOBLE METAL RESTORATIONS).

MINUTES

Health Evidence Review Commission's
Oral Health Advisory Panel (OHAP)

Clackamas Community College
Wilsonville Training Center, Room 210
November 28, 2016
10:00 AM – 1:00 PM

Members Present: Gary Allen, DMD, Chair; Bruce Austin, DMD (via phone); Deborah Loy; Mike Shirtcliff, DMD; Gary Allen, DMD; Lori Lambright (via phone); Patricia Parker, DMD (via phone); Karen Nolan; Eli Schwarz, DDS, MPH, PhD; Len Barozzini, DDS; Lynn Ironside

Members Absent: Mike Plunkett, DMD

Staff Present: Darren Coffman; Ariel Smits, MD, MPH; Cat Livingston, MD, MPH

Also Attending: Kellie Skenandore, OHA; Kathleen Olesitse, CareOregon Dental (via phone); Lori McKeane, AllCare; Heather Simmons, Pacificsource (via phone), Dayna Steringer, DK Stat/ Advantage Dental.

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

The meeting was called to order at 10:02 am and roll was called. The minutes from the September, 2016 meeting were reviewed and minor corrections made. Coffman reviewed the purpose of the meeting.

- **Topic: Multisector intervention: Early Childhood Caries Prevention**

Cat Livingston introduced the concept of multisector interventions and reviewed the draft scope statement for the multisector intervention statement for *Early Childhood Caries Prevention*. Schwarz recommended looking at motivational interviewing/anticipatory guidance. Loy wondered whether the question should include children up to age 6; she felt that it should be limited to younger children (pre-school and younger). It was clarified that children under age 6 means children 5 and younger. Schwarz pointed out that much of the literature on early childhood caries examines children age 3 and younger. The group was generally okay with children up to their 6th birthday; the term used should be consistent in the report.

The group discussed breaking out pregnant women as a separate report, looking at all interventions to improve dental health in pregnant women. Livingston discussed that

multisector interventions can include interventions outside of typical (child-targeted, clinical) interventions and thus xylitol in pregnancy would be appropriate to include as well as other types of interventions such as community-oriented ones. Allen suggested clarifying that the counseling would also include counseling of pregnant women as well as parents of small children. Schwarz recommended looking at extending coverage of dental care beyond the immediate postpartum period as another intervention. Loy mentioned that there is an oral health in pregnancy consensus statement that has already been prepared by the National Maternal and Child Oral Health Policy Center. It was noted to be available on the Oregon Oral Health Coalition website. Shirtcliff noted that the consensus statement is evidence based and has references to all of the literature reviewed.

The panel discussed that the dental group has done an extensive evidence review of early childhood caries several years ago. Livingston reviewed that a multisector intervention would become part of the Prioritized List and would be available to the CCOs and other audiences larger than the dental community. It could result in interventions outside of the typical ICD-10/CPT code pairings or CDT codes. Schwarz expressed reservations about the actual strength of evidence behind many dental interventions.

Livingston discussed creating a report that lists interventions with good evidence to support them. There was some discussion about those interventions, like fluoride toothpaste, which may not be studied because they are so obviously helpful. Livingston noted this and will consider how to present this type of intervention in the report.

Simmons wondered about having codes to implement the multisector interventions. Livingston clarified that many of the multisector interventions are unlikely to have codes, and CCOs and others would choose whether or not to invest discretionary spending in these types of interventions. The tobacco multisector intervention was discussed again as a menu of evidence-based options for CCOs to help achieve their performance metric.

Schwarz talked about addressing early childhood caries through a multisector intervention statement as having value for Oregon. Five to seven other states have their own guidelines (e.g. California, Michigan, and New York). Also, a multisector intervention statement is a key linkage to the public health world. The group agreed it was worth proceeding.

Livingston clarified that toothbrushing and flossing are not in the scope of this statement; in contrast, toothbrushing programs (with or without fluoridated toothpaste) would be included within the scope. Len asked whether including unfluoridated toothpaste within toothbrushing programs was appropriate, and others clarified that programs showing differential effectiveness based on the use of fluoridated versus unfluoridated toothpaste could be helpful, and could potentially result in a recommendation against unfluoridated toothpaste campaigns. Livingston asked whether she should look at prescription strength fluoridated toothpaste and the group did not think this would be useful.

The group reviewed the proposed outcomes. They felt that caries as an outcome was insufficient, and identified more important outcomes of being "cavity-free" and reducing the rate of cavities. They also clarified that dmfs should be used instead of DMFS.

The group turned to a discussion of "overall visits" as an outcome measure. The goal is to prevent certain types of preventable visits (e.g., hospitalization, dental surgery under anesthesia). Barozzini discussed that dental visits should go up and Shirtcliff discussed that there should be a general increase in visits that result in prevention, regardless of where the patient shows up. The group decided to eliminate the outcome of dental visits and focus on the undesirable visits (i.e., ED visits, dental hospitalizations, and oral surgeries).

Loy raised the issue of targeting siblings at the time of oral surgery or hospitalization. Many siblings of kids with cavities will also be at high risk, and studies show intervening can help.

The group discussed whether or not to add the use of antibiotics and opioids to the outcomes. Schwarz said that the studies are going to be older and there will be no evidence about opioids. The group directed staff to look at these only if they were to show up in the harms.

Schwarz raised that Key Question 2e did not accurately capture the intent, and they struck the bullet.

Barozzini raised the issue of making sure that breastfeeding was not discouraged as part of early childhood caries prevention. The group talked about the importance of baby bottle tooth decay and not having constant sugary drink consumption in bottles. Barozzini discussed that breastfeeding helps to prevent this, and the group decided to amend the scope statement to include this.

Contextual question 2 discusses risk assessment tools, and the group clarified the mostly useful one of these would be for risk assessment outside of the dental office.

The age range was again discussed and the group chose to stay with under 6 because it mirrors what is in the OARs, but given the ongoing concern about the language, Livingston offered to add 5 and under parenthetically for greater clarity.

Livingston said she would revise the scoping statement and send it out to the group. The evidence review will be completed internally by HERC staff. The review will not be ready for the February 2017 OHAP meeting and will be reviewed at a future OHAP meeting in 2017.

Recommended Actions:

1) Livingston will send out the revised PICO and key questions via email to the group for review
2) Livingston to work on the multisector intervention evidence review and bring it back to a 2017 OHAP meeting for further review and discussion

➢ **Topic: Guideline Note 17: Preventive Dental Care**

Smits reviewed the request to clarify "high risk" in GN17. The OHAP members had received several documents with information about dental risk. Shirtcliff brought up the new CDT risk codes (D0601-D0603), which were introduced to assist in identifying high risk patients. The group felt that high risk should be defined as CDT D0603 (Caries risk assessment and documentation with a finding of high risk) in a billing statement. If D0603 appears on a bill for fluoride or prophylactic care, then a higher frequency of claims for that patient should be allowed. Kellie Skenandore will look into whether D0603 can be used as a secondary code for billing. Shirtcliff noted that DCOs would still need to do chart audits to determine whether they were coded correctly as high risk. This was acknowledged. Allen felt this change would be helpful, and that the use of D0603 should be encouraged.

Recommended Actions:

1) No change to GN17
2) Skenandore will look into operationalizing the use of D0603 as a secondary code to allow identification of high risk patients

➢ **Topic: Guideline Note 34: Oral Surgery**

Smits reviewed the topic summary. The OHAP members felt the revised guideline was much improved. Loy suggested that OHAP might look at old HSD rules that defined severe dental pain. She believed the old rules included such items as: not responsive to OTC meds, keeps you up at night, etc. An "or" was added to clause #2 to clarify that a patient only needed one of the three entries to qualify for impacted third wisdom tooth removal. It was noted that non-impacted wisdom teeth could be removed if they met criteria for extraction of any other tooth (i.e. multiple caries, infection, etc.).

Recommended Actions:

1) GN34 was modified as shown below:

GUIDELINE NOTE 34, ~~ORAL SURGERY~~ EXTRACTION OF IMPACTED WISDOM TEETH

Line 349

~~Treatment only for symptomatic dental pain, infection, bleeding or swelling (D7220, D7230, D7240, D7241, D7250).~~

Extraction of impacted wisdom teeth (D7220, D7230, D7240, D7241, D7250) is only included on this line when there is:

1) evidence of pathology. Such pathology includes unrestorable caries, non-treatable pulpal and/or periapical pathology, cellulitis, abscess and osteomyelitis, internal/external resorption of the tooth or adjacent teeth, fracture of tooth, disease of follicle including cyst/tumor, tooth/teeth impeding surgery or reconstructive jaw surgery, and when a tooth is involved in or within the field of tumor resection OR

2) two or more episodes of pericoronitis OR
3) severe pain directly related to the impacted tooth that does not respond to conservative treatment.
    a. extraction for pain or discomfort related to normal tooth eruption or for non-specific symptoms such as "headaches" or "jaw pain" is not considered medically or dentally necessary for treatment.

- **Topic: 2018 Biennial Review: Dental Implant Removal**

Smits reviewed the summary document regarding possible addition of coverage for some or all dental implant CDT codes. Shirtcliff and Parker both supported coverage for the removal of infected implants. Allen pointed out that the CDT code for implant removal (CDT D6100 IMPLANT REMOVAL, BY REPORT) is currently on an uncovered line. Parker and Allen reported that their DCOs are covering implant removal as a needed services, even if they are not reimbursed for it. Loy cautioned that adding coverage for removal of an implant is a slippery slope that might add costs to the DCOs that are more appropriately borne by the medical plans. Nolan suggested that if implant removal is covered, then the DCO rates should be reassessed. Shirtcliff reflected that OHAP should consider coverage for implant placement as well, as current OHP policy results in patients being made edentulous to allow dentures when some teeth could have been saved if implants were covered. Other OHAP members felt that implant placement should be covered only after crowns are covered, as crowns are a more important service. There was general agreement that implant removal should be covered, but not placement. Debridement of implants was discussed, but this was felt to be covered with general scaling of the other teeth. Specific treatment of implants is problematic in terms of what dental professional is responsible (the placing oral surgeon, the treating dentist, etc.). There was concensus that the addition of implant removal should be a biennial review change, to allow the normal rate review process to occur. Implementation of this benefit would then be January 1, 2018. There was also consensus that a guideline for when implant removal would be covered should be drafted, to follow similar situations to the newly adopted guideline for removal of impacted third molars.

Recommended Actions:

1) 2018 Biennial review change:
    a. Add CDT D6100 (IMPLANT REMOVAL, BY REPORT) to line 349 DENTAL CONDITIONS (EG. SEVERE CARIES, INFECTION) Treatment: ORAL SURGERY (I.E. EXTRACTIONS AND OTHER INTRAORAL SURGICAL PROCEDURES)
    b. Smits and Allen to draft a guideline for when implant removal is included on that line and send to OHAP members for review
    c. Further discussion of the guideline will occur at the February, 2017 OHAP meeting

- **Topic: 2018 Biennial Review: Oral Health**

HERC staff reviewed that the 2018 biennial review was currently underway. The dental lines with all codes had been included in the meeting packet for members to review. Staff asked if there was any suggestions for oral health biennial review topics to take up, other than the addition of implant removal.

There was some discussion regarding the counseling CDT codes (D9311, D9991-D9994) that were discussed at the last meeting and added to the HSD Ancillary File. There was a question about adding these to lines to allow more visibility and utilization. The discussion about this centered around lack of clarity in what these codes will be used for, the provider types that can use these codes, etc. The decision was to wait and re-evaluate these codes at a later date once these questions are answered.

Allen brought up possibly adding coverage for immediate partial dentures (CDT D5221-D5222), based on provider request for the addition of this service. Currently, standard and interim partial dentures are covered on line 457. The discussion centered on how to define immediate. The members questioned whether there were any issues with immediate dentures, such as less durability than an interim denture which can last 5 years. Allen thought that an immediate partial denture would be a longer term solution than an interim denture. One of the issues is that dentists feel it is unethical to code for a standard partial denture (not immediate) when an immediate partial denture was actually provided. There were concerns about lack of allowed healing if immediate partial dentures were fitted very soon after an anterior tooth extraction. Some DCO plans are paying for an interim partial denture and then a standard partial denture, while others are only covering one or the other every 5 years. Cost are about the same for immediate and interim partial dentures.

The consensus was that immediate partial dentures should be added to line 457, where interim and standard partial dentures CDT codes already are placed. The DCOs and/or HSD could make rules about whether an immediate partial denture could be followed by a standard partial denture placement, and other utilization rules.

There was discussion that adding immediate partial dentures may add significant cost, and this change was best done as a biennial review change, effective January 1, 2018.

One last biennial review topic was brought up by Barozzini. He would like to clarify coverage of D9110 PALLIATIVE (EMERGENCY) TREATMENT OF DENTAL PAIN-MINOR PROCEDURES. There was some discussion about whether palliative emergency treatment would include prescribing antibiotics. It was unclear what services were allowed with this code. This code will be considered at a later time if there are continued questions or issues.

HERC staff let the members know that biennial review topics can be nominated for consideration at the planned February OHAP meeting. All topics to be nominated must be to HERC staff by 12/30/16.

Recommended Actions:

1) 2018 Biennial review: add D5221-D5222 (Immediate partial denture – resin base) to line 457 DENTAL CONDITIONS (EG. MISSING TEETH, PROSTHESIS FAILURE) Treatment: REMOVABLE PROSTHODONTICS (E.G. FULL AND PARTIAL DENTURES, RELINES) and removed from line 594 DENTAL CONDITIONS (EG. CARIES, FRACTURED TOOTH) Treatment: ADVANCED RESTORATIVE-ELECTIVE (INLAYS,ONLAYS, GOLD FOIL AND HIGH NOBLE METAL RESTORATIONS).
2) HSD to determine rules about how often any type of partial denture can be covered and in what situations immediate partial dentures would be covered (i.e. anterior tooth extraction).

- **Topic: Tooth Extraction for Severe Caries**

Approved with minimal discussion.

Recommended Actions:

1) Add K02 series (Dental caries) to line 349 DENTAL CONDITIONS (EG. SEVERE CARIES, INFECTION) Treatment: ORAL SURGERY (I.E. EXTRACTIONS AND OTHER INTRAORAL SURGICAL PROCEDURES)
2) Add D7210 (SURGICAL REMOVAL OF ERUPTED TOOTH REQUIRING REMOVAL OF BONE AND/OR SECTIONING OF TOOTH, AND INCLUDING ELEVATION OF MUCOPERIOSTEAL FLAP IF INDICATED) to line 349

- **Public Comment:**

No additional public comment was received.

- **Issues for Next Meeting:**

- Guideline for implant removal
- Any other oral health biennial review topics
- Multisector intervention for early childhood caries prevention (post-February meeting)

- **Next Meeting:**
  - TBD

Meeting was adjourned at 12:45 PM.

Section 4.0

Consent Agenda-

Straightforward Items

Consent Agenda Issues—February, 2017

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
41015 41016 41017 41018	Extraoral incision and drainage of abscess, cyst, or hematoma of floor of mouth; sublingual submental submandibular masticator space	210 SUPERFICIAL ABSCESSES AND CELLULITIS	HSD requested that 41017 pair with K12.2 (Cellulitis and abscess of mouth). 41017 is on lines 168, 600. The entire series 41015-41018 is also appropriate to pair.	Add 41015-41018 to line 210
14301	Adjacent tissue transfer or rearrangement, any area; defect 30.1 sq cm to 60.0 sq cm	172 COMPLICATED HERNIAS; UNCOMPLICATED INGUINAL HERNIA IN CHILDREN AGE 18 AND UNDER; PERSISTENT HYDROCELE	HSD requested 14301 to pair with K43.0 (Incisional hernia with obstruction, without gangrene. 14301 is currently on many lines.	Add 14301 to line 172
15734	Muscle, myocutaneous, or fasciocutaneous flap; trunk	172 COMPLICATED HERNIAS; UNCOMPLICATED INGUINAL HERNIA IN CHILDREN AGE 18 AND UNDER; PERSISTENT HYDROCELE	HSD requested 15734 to pair with K43.0 (Incisional hernia with obstruction, without gangrene). 15734 is on lines 204, 212, 234, 259, 280, 292, 319, 384	Add 15734 to line 172
44300	Placement, enterostomy or cecostomy, tube open (eg, for feeding or decompression)	383 ESOPHAGEAL STRICTURE; ACHALASIA	HSD requested that 44500 pair with K22.2 (Esophageal obstruction). 44500 is on lines 32,46,51,75,92,105,161,319,383.	Add 44500 to line 383
43270	Esophagogastroduodenoscopy, flexible, transoral; with ablation of tumor(s), polyp(s), or other lesion(s) (includes pre- and post-dilation and guide wire passage, when performed)	60 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE	HSD requested that 43270 pair with K31.819 (Angiodysplasia of stomach and duodenum without bleeding). Previously, this procedure was coded with 43258, which is no longer a valid code. 43270 is on lines 319,595,642. Similar codes are on line 60	Add 43270 to line 60
K51.4	Inflammatory polyps of colon without complications	32 REGIONAL ENTERITIS, IDIOPATHIC PROCTOCOLITIS, ULCERATION OF INTESTINE 170 ANAL, RECTAL AND COLONIC POLYPS	HSD requested that K51.4 pair with 45385 (removal of polyp) which is on 5 lines including line 170. K51.4 is more appropriately on line 170.	Remove K51.4 from line 32 Add K51.4 to line 170

Consent Agenda Issues—February, 2017

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
43270	Esophagogastroduodenoscopy, flexible, transoral; with ablation of tumor(s), polyp(s), or other lesion(s) (includes pre- and post-dilation and guide wire passage, when performed)	60 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE	HSD requested that 43270 pair with K26.9 (Duodenal ulcer, unspecified as acute or chronic, without hemorrhage or perforation). 43270 is used for destruction of lesions that are not currently bleeding.	Add 43270 to line 60
44346	Revision of colostomy; with repair of paracolostomy hernia	172 COMPLICATED HERNIAS; UNCOMPLICATED INGUINAL HERNIA IN CHILDREN AGE 18 AND UNDER; PERSISTENT HYDROCELE	HSD requested that 44346 pair with K43.3 (Parastomal hernia with obstruction, without gangrene). 44346 is currently on lines 92,105,161,428,531.	Add 44346 to line 172
21210	Graft, bone; nasal, maxillary or malar areas (includes obtaining graft)	305 CLEFT PALATE AND/OR CLEFT LIP	21210 added to line 305 in error in November, 2016. HSD is requesting that we reverse this decision.	Remove 21210 from line 305
Z15.01 Z15.02	Genetic susceptibility to malignant neoplasm of breast Genetic susceptibility to malignant neoplasm of ovary	195 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER	ICD-10 Z15.01 and Z15.02 are currently informational. They are used for genetic testing and various treatment for women who are BRCA+. Line 195 has a GN regarding BRCA positive or other genetically high risk women.	Add Z15.01 and Z15.02 to line 195

Non-Congenital Diaphragmatic Hernia Repair

Question: What procedures should pair with diaphragmatic hernias?

Question source: HSD, Walter Hardin, MD, OHP Medical Director

Issue: Diaphragmatic hernias were reviewed in March, 2016, and moved from the GERD line to the hernia line when obstructed or gangrenous (ICD-10 K44.0 (Diaphragmatic hernia with obstruction, without gangrene) and K44.1 (Diaphragmatic hernia with gangrene)). Uncomplicated diaphragmatic hernias (ICD-10 K44.9) was kept on the uncovered GERD line. Several CPT codes were moved to the complicated hernia line to allow repair; however, it appears that several other CPT codes are required to be moved that were not identified in the previous review in order to allow treatment of this condition.

Current code placement

Code	**Description**	**Line**
43281	Laparoscopy, surgical, repair of paraesophageal hernia, includes fundoplasty, when performed; without implantation of mesh	385 ESOPHAGITIS; GERD
43282	with implantation of mesh	385
43283	Laparoscopy, surgical, esophageal lengthening procedure (eg, Collis gastroplasty or wedge gastroplasty) (List separately in addition to code for primary procedure)	68 CONGENITAL ANOMALIES OF UPPER ALIMENTARY TRACT, EXCLUDING TONGUE

HERC staff recommendation:

1) Add 43281-43283 to line 172 COMPLICATED HERNIAS; UNCOMPLICATED INGUINAL HERNIA IN CHILDREN AGE 18 AND UNDER; PERSISTENT HYDROCELE
    a. Do not add to line 516 ESOPHAGITIS AND GERD; ESOPHAGEAL SPASM; ASYMPTOMATIC DIAPHRAGMATIC HERNIA
        i. Asymptomatic diaphragmatic hernias do not require repair

Section 5.0

Biennial Review

Prioritization of the treatment of chronic hepatitis C

Question: How should treatment of early stages of chronic hepatitis C be prioritized?

Question source: Pharmacy & Therapeutics Committee, OHA Leadership

Issue:
At the November 2016 HERC meeting commissioners discussed a plan to address the treatment of chronic hepatitis C at a future meeting. The Pharmacy & Therapeutics Committee had been reviewing coverage of DAAs (direct acting antivirals such as sofosbuvir) and were considering potentially expanding coverage to F2. The decision was made to have HERC weigh in on prioritization of treatment. HERC members discussed a potential two-step process: 1) complete a review about stage 2 prioritization to meet the deadline for the current biennial review in March and then 2) a review of stages 0 and 1 after that, which may need to be incorporated into the 2019 biennial review depending on what types of changes are made.

OHA has submitted a specific budget request to allow for extra funds to support expansion of coverage for hepatitis C for fibrosis stage 2 (the outcome of this will be determined at some point during the legislative session).

Staff would propose the following questions as primary drivers of the decision about prioritizing treatment for chronic hepatitis C:

1) Is it relatively safe to prioritize those with more advanced disease higher?
2) Are there harms emerging about the treatment with DAAs that may affect the benefit/harm balance?
3) Does cost-effectiveness differ between earlier and later stages of fibrosis?
4) What is the overall impact on the budget (given the cost and the prevalence) and how may this impact coverage of other health care or non-health care services?

The following assumptions by staff have been made:

1) F3 and F4 are currently covered for the OHP population through prior P&T decisions and F2 in select circumstances. Therefore, for the purposes of this review, coverage of F3 and F4 are assumed.
2) Treating at various stages of disease will yield roughly similar rates of SVR12 (sustained viral response at 12 weeks, the outcome used by the literature) e.g. we do not expect that treating F4 would result in a 90% SVR12 while treating at F2 would result in a 50% SVR12. We are assuming that they will generally be in the same ballpark. Most of the studies do not differentiate between various degrees of non-cirrhotic fibrosis levels (stages other than F4).
3) That SVR12 via DAAs is a reasonable proxy for long-term improvements - this is the widely accepted belief about the DAAs, although not the same standard to which we generally hold other interventions. All of the studies use SVR12 as the primary outcome and not other patient-oriented outcomes (like decompensated cirrhosis and hepatocellular carcinoma).

Prioritization of the treatment of chronic hepatitis C

Current Prioritized List Status:

Line: 203

Condition: CHRONIC HEPATITIS; VIRAL HEPATITIS (See Guideline Notes 64,65,76)
Treatment: MEDICAL THERAPY
ICD-10: B15.0-B15.9,B16.0-B16.9,B17.0,B17.10-B17.9,B18.0-B18.9,B19.0,B19.10-B19.9,B25.1,K73.0-K73.9,K74.1-K74.2,K75.4,K75.81,K76.0,K76.4
CPT: 91200,96150-96155,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99449,99468-99480,99487-99498,99605-99607
HCPCS: G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508, G0509

Line: 246

Condition: ACUTE AND SUBACUTE NECROSIS OF LIVER; SPECIFIED INBORN ERRORS OF METABOLISM (EG. MAPLE SYRUP URINE DISEASE, TYROSINEMIA)
Treatment: LIVER TRANSPLANT
ICD-10: D81.810,D84.1,E70.20-E70.29,E70.330-E70.331,E70.5-E70.9,E71.0,E71.110-E71.2,E72.10-E72.29,E72.52-E72.53,E72.8,E74.00-E74.09,E80.5,E83.00-E83.10,E83.110-E83.19,K72.00-K72.01,K73.1-K73.8,K76.2,T86.40-T86.49, Z48.23,Z52.6
CPT: 47133-47147,86825-86835,96150-96155,97802-97804,98966-98969, 99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404, 99408-99449,99468-99480,99487-99498,99605-99607
HCPCS: G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508, G0509

Line: 339

Condition: ALCOHOLIC FATTY LIVER OR ALCOHOLIC HEPATITIS, CIRRHOSIS OF LIVER (See Guideline Notes 64,65,77)
Treatment: MEDICAL THERAPY
ICD-10: K70.0,K70.10-K70.9,K71.3-K71.4,K71.50-K71.7,K72.10-K72.91,K74.0,K74.3-K74.5,K74.60-K74.69,K76.1,K76.6,K76.89
CPT: 37182,37183,96150-96155,97802-97804,98966-98969,99051,99060,99070, 99078,99184,99201-99239,99281-99285,99291-99404,99408-99449, 99468-99480,99487-99498,99605-99607
HCPCS: G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508, G0509

GUIDELINE NOTE 76, DIAGNOSTIC TESTING FOR LIVER FIBROSIS TO GUIDE TREATMENT OF HEPATITIS C IN NON-CIRRHOTIC PATIENTS

Line 203

If a fibrosis score of ≥F2 is the threshold for antiviral treatment of Hepatitis C, the following are included on this line:

Imaging tests:

- Transient elastography (FibroScan®)
- Acoustic radiation force impulse imaging (ARFI) (Virtual Touch™ tissue quantification, ElastPQ)
- Shear wave elastography (SWE) (Aixplorer®)

Blood tests (only if imaging tests are unavailable):

- Enhanced Liver Fibrosis (ELF™)
- Fibrometer™
- FIBROSpect® II

If a fibrosis score of ≥F3 is the threshold for antiviral treatment of Hepatitis C, one or more of the following are included on this line:

Imaging tests:

- Transient elastography (FibroScan®)
- Acoustic radiation force impulse imaging (ARFI)
- Shear wave elastography (SWE)

Magnetic resonance elastography is included on this line for ≥F2 or ≥F3 only when at least one imaging test (FibroScan, ARFI, and SWE) has resulted in indeterminant results, a second one is similarly indeterminant, contraindicated or unavailable, and MRE is readily available.

Noninvasive tests are covered no more often than once per year.

The development of this guideline note was informed by a HERC Coverage Guidance. See http://www.oregon.gov/oha/herc/Pages/blog-liver-fibrosis.diagnosis.aspx

ICD 10 Code	Code Description	Line Placement
B17.10	Acute hepatitis C without hepatic coma	203
B17.11	Acute hepatitis C with hepatic coma	203
B17.8	Other specified acute viral hepatitis	203
B17.9	Acute viral hepatitis, unspecified	203
B18.2	Chronic viral hepatitis C	203
B19.20	Unspecified viral hepatitis C without hepatic coma	203
B19.21	Unspecified viral hepatitis C with hepatic coma	203
B19.9	Unspecified viral hepatitis without hepatic coma	203

ICD 10 Code	Code Description	Line Placement
K73.0	Chronic persistent hepatitis, not elsewhere classified	203
K73.1	Chronic lobular hepatitis, not elsewhere classified	203,246
K73.2	Chronic active hepatitis, not elsewhere classified	203,246
K73.8	Other chronic hepatitis, not elsewhere classified	203,246
K73.9	Chronic hepatitis, unspecified	203
K74.0	Hepatic fibrosis	339
K74.1	Hepatic sclerosis	203
K74.2	Hepatic fibrosis with hepatic sclerosis	203

Oregon Pharmacy & Therapeutics Committee Medicaid PA criteria (see full document)
Treatment is limited to F3 or F4 with a few exceptions.
Exceptions are made for

1. Extrahepatic manifestations
    a. Type 2 or 3 cryoglobulinemia with end organ manifestations (i.e. leukocytoclastic vasculitis)
    b. Proteinuria, nephrotic syndrome or membranoproliferative glomerulonephritis
    c. Porphyria cutanea tarda
2. Co-infection with HIV
3. Transplant patients (pre or post)
    a. Listed for transplant and it is essential to prevent recurrent hepatitis C infection post-transplant; or
    b. Post solid organ transplant

Definitions (From MED, 2016 report)

Table 1. METAVIR Fibrosis Scores

METAVIR Score	Description
F0	No fibrosis (normal liver)
F1	Portal fibrosis without septa*
F2	Portal fibrosis with few septa*
F3	Numerous septa without cirrhosis (includes developing cirrhosis)
F4	Cirrhosis

*The term "bridging fibrosis" is equal to "septa" in the Ishak score. Scheuer fibrosis grades are similar to Metavir scores.

Length of time in fibrosis stages

MED, 2017

- *A*pproximately 20% of patients with acute hepatitis C infection will clear their acute infection.
- If patients go on to develop chronic hepatitis C, liver fibrosis from HCV (hepatitis C virus) progresses slowly.
- In a 20- to 30-year period, 5% to 20% of people with HCV will develop cirrhosis, and 1% to 5% will die from cirrhosis or liver cancer. These may be overestimates because the populations included in these studies had many confounding comorbidities.
- *Konerman, 2014*
    - Systematic review of 29 longitudinal studies including 5,817 patients, mostly younger men 30-50 without coinfections. The incidence of fibrosis progression on follow-up biopsy ranged from 21% to 61% in a follow-up period of 2.5 to 10 years using an increase of more than one Metavir fibrosis stage (F0-F4) as the criterion for progression. Progression from compensated to decompensated cirrhosis ranged from 13% to 40% during a range of 2.3 to 14.3 years, and overall mortality ranged from 8% to 47% in 3.9 to 14.4 years.

- *Thein, 2008*
    - Systematic review of prognostic studies published between 1990 and 2007
    - 111 studies (33,121 patients); 100 cross-sectional studies, 11 retrospective cohort studies, 97 clinical setting studies (e.g. liver clinics); and 14 non-clinical setting (e.g., screening programs)

Table 2. Estimated Annual Mean Transition Probabilities by Fibrosis Stage

Transition of Metavir Fibrosis Stage	Annual Mean Transition Probability (95% CI)
F0 -> F1	0.117 (0.104 to 0.13)
F1 -> F2	0.085 (0.075 to 0.096)
F2 -> F3	0.12 (0.109 to 0.133)
F3 -> F4	0.116 (0.104 to 0.129)

Note. 95% CI indicates 95% confidence interval.

- Older studies (before 2000) showed a higher probability of developing cirrhosis

- *Butt, 2015*
  - Longitudinal cohort study of veterans
  - Used an inception cohort (negative HCV to positive) of 1840 patients and matched them to 1840 HCV negative patients
  - HCV patients more likely to be younger and have drug and alcohol problems
  - Progression started early but then tapered off after 5 years
  - After 10 years more HCV positive patients than HCV negative patients had cirrhosis (18.4% versus 6.1%); and 9 years after cirrhosis developed, decompensated cirrhosis occurred more often in HCV positive patients (1.79% v 0.33%). All statistically significant.
- *Huang, 2015*
  - Single institution longitudinal study of 1,033 patients in Australia, all who had liver biopsies
  - Linked biopsy data with clinical outcomes data from statewide data systems
  - Liver related survival probability was not significantly different between patients with F0, F1, or F2. Patients with F0–F2 fibrosis also had higher HCC-free and hepatic decompensation-free survival probability (Table 1). In contrast, survival probability was significantly lower for patients with F3 and F4 fibrosis: The age-adjusted hazard ratio for F3 (versus F0–F2) was 4.24 (95% CI, 1.6 to 10.9) and for F4 was 23.0 (95% CI, 10.7 to 49.6).

Table 1. Estimates of Survival by Metavir Score

Metavir score	Fibrosis stage on initial liver biopsy N (%)	18-year survival probability (95% CI)	15-year HCC-free survival (95% CI)	15-year hepatic decompensation-free survival (95% CI)
F0	173 (20)	99% (96–100%)	100%	100%
F1	383 (44)	96% (91–98%)	99% (98–100%)	96% (93–98%)
F2	124 (14)	94% (83–98%)	98% (92–100%)	94% (86–97%)
F3	80 (9)	77% (51–91%)	78% (52–91%)*	86% (70–94%)*
F4	73 (8)	40% (23–57%)**	78% (62–88%)†	58% (44–70%)†

* 18-year HCC-related and hepatic decompensation-free survival probability

** 15-year survival probability

† 10-year survival probability

- *Zeremski, 2016*
  - 378 hepatitis C patients at New York City Hospital, all patients had to have 2 liver biopsies

- The estimated time spent in a fibrosis stage was shortest for fibrosis Stage 0 (2.55 years; 95% CI, 1.61 to 4.04 years) and longest for Stage F2 (18.4 years; 95% CI, 11.5 to 29.4 years)

- Xu, 2016
  - Cohort study of 2799 patients in 4 large integrated health systems in US
  - 54% received interferon based treatment

Table 3. One- and Five-Year Probabilities of Clinical Outcomes by Fibrosis Stage

Metavir Fibrosis Stage* N (%)	Follow-up Period	Hepatic Decompensation % (95% CI)	HCC % (95% CI)	Liver Transplant % (95% CI)	All-cause Mortality % (95% CI)
F0-F1 1033 (40%)	1 year	0.4 (0.2 to 1.1)	0	0.1 (0.01 to 0.6)	1.5 (0.9 to 2.4)
	5 years	2.3 (1.3 to 3.8)	0	0.3 (0.06 to 1.1)	6.8 (5.0 to 9.0)
F2 849 (30%)	1 year	1.1 (0.5 to 2.2)	0.1 (0.01 to 0.7)	0.1 (0.01 to 0.8)	1.7 (0.9 to 2.8)
	5 years	3.5 (2.1 to 5.5)	1.2 (0.4 to 2.8)	0.4 (0.1 to 1.4)	6.9 (4.7 to 9.5)
F3 509 (18%)	1 year	4.0 (2.4 to 6.3)	1.7 (0.7 to 3.3)	0.2 (0.01 to 1.1)	4.8 (3.0 to 7.3)
	5 years	18.6 (13.5 to 24.4)	3.3 (1.6 to 6.2)	2.4 (0.7 to 6.2)	13.7 (9.4 to 18.9)
F4 408 (14%)	1 year	13.4 (10.0 to 17.3)	4.8 (2.8 to 7.4)	1.6 (0.6 to 3.4)	8.0 (5.4 to 11.3)
	5-year	33.6 (27.7 to 39.5)	11.7 (8.0 to 16.1)	6.5 (3.8 to 10.2)	31.5 (25.6 to 38.2)

Harms
MED, 2017

- No comparative or cohort studies that reported long-term harms of DAAs.
- Case reports suggest that DAAs could cause reactivation of hepatitis B virus (HBV) in patients who have HCV/HBV coinfections; these reports resulted in a U.S. Food and Drug Administration (FDA) black box warning. 28 cases of reactivation of hepatitis B have been reported. (Patients with HBV coinfection were excluded from the approval trials).
- Cases have been reported of accelerated decompensation and death in patients with moderate to severely decompensated cirrhosis who have taken DAAs, and a drug approval study was stopped because of cardiotoxicity from a DAA with a pharmacological structure similar to sofosbuvir.
- There is the possibility of inducing resistance
- Only one recent systematic review examined the harms or adverse events of the new DAAs and focused on the conditions that would have the most influence on quality of life and resource use: rash, anemia, and depression. Indirect comparisons from a network meta-analysis found that, in general, fewer patients who took DAAs had rashes, anemia, and depression compared to interferon-based regimens. Other common adverse events were fatigue, headaches, and insomnia, but these were generally mild to moderate and caused few people to discontinue treatment.

Cost-effectiveness analyses

Limited to US based analyses published in 2015 or later, that stratified by fibrosis stage, and available as full text

Chahal, 2016 Article not included due to length; available online.

1. Population – treatment naïve population, genotype 1; compared 6 HCV treatment options versus no treatment

2. RESULTS: Simulated 1000 individuals, but present the results normalized to a single HCV-infected person. In the base-case analysis, among patients receiving 8 or 12 weeks of sofosbuvir-ledipasvir treatment, treating all fibrosis stages compared with treating stages F3 and F4 adds 0.73 QALYs and $28 899, for an ICER of $39 475 per QALY gained. Treating at stage F2 (portal fibrosis with rare septa) costs $19 833 per QALY gained vs waiting until stage F3; treating at stage F1 (portal fibrosis without septa), $81 165 per QALY gained compared with waiting until stage F2; and treating at stage F0, $187 065 per QALY gained compared with waiting until stage F1. Results for other regimens show a similar pattern. At base-case drug prices, treating 50% of all eligible US patients with HCV genotype 1 would cost $53 billion. Patients older than age 70 had an ICER of greater than $100,000.

Chhatwal, 2015 Article not included due to length; available online

1. Population - treatment naïve and treatment experienced, lifetime time horizon; 3rd party payer perspective, sofosbuvir and ledipasvir; comparison – old standard of care.

2. Results: Sofosbuvir-based therapies added 0.56 QALY relative to the old standard of care (oSOC), at an incremental cost of $55 400 per additional QALY. The ICERs ranged from $9700 to $284 300 per QALY depending on the patient's status with respect to prior treatment, HCV genotype, and the presence of cirrhosis. At $100 000 willingness-to-pay per QALY, sofosbuvir-based therapies were cost-effective in 83% of treatment-naive and 81% of treatment-experienced patients.
3. Compared with the oSOC, new drugs would cost an additional $65 billion in the next 5 years to treat eligible HCV-infected people in the United States, whereas the resulting cost offsets would be $16 billion.

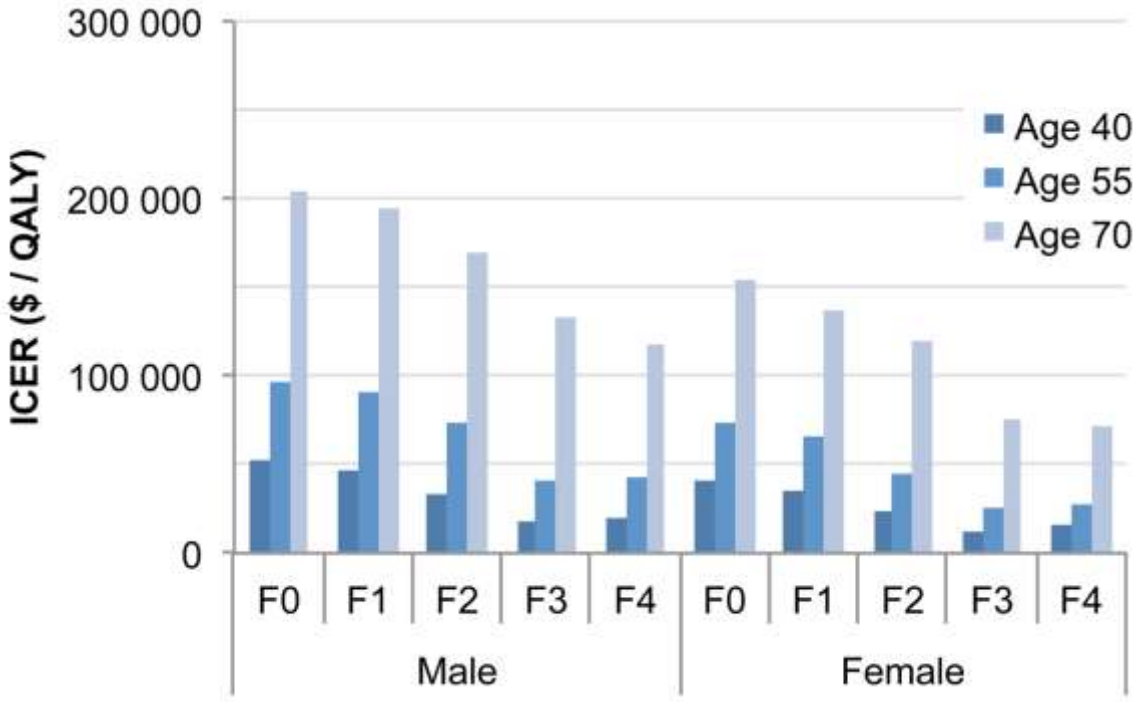


Figure 5.
Incremental cost-effectiveness ratios (ICERs) of sofosbuvir- and ledipasvir-based therapies by fibrosis score (F0–F4), sex, and age.
Abbreviations: F0–F4, METAVIR fibrosis scores. Note that ICERs of males were higher than those of females because of higher background mortality of males than females.

Linas, 2015 Article not included due to length; available online.

1. Population – focus on genotypes 2 and 3, sofosbuvir-based regimens

2. **Results of a Base-Case Analysis:** The ICER of sofosbuvir-based treatment was less than $100 000 per QALY in cirrhotic patients (genotype 2 or 3 and treatment-naive or treatment-experienced) and in treatment-experienced noncirrhotic patients but was greater than $200 000 per QALY in treatment-naive noncirrhotic patients.
3. Among treatment-naive noncirrhotic patients, we also investigated cost-effectiveness by disease stage and found that in those with METAVIR stage F3 disease, the ICERs of 12 weeks of sofosbuvir–ribavirin for genotype 2 treatment and 12 weeks of pegylated interferon– ribavirin–sofosbuvir for genotype 3 treatment were less than $100 000 per QALY gained compared with pegylated

interferon–ribavirin. However, in patients with stage F0 to F2 disease, the ICER of sofosbuvir-based regimens was more than $100 000 per QALY gained compared with pegylated interferon–ribavirin.

4. **Author Conclusions:** Sofosbuvir provides good value for money for treatment-experienced patients with HCV genotype 2 or 3 infection and those with cirrhosis. At their current cost, sofosbuvir-based regimens for treatment-naive noncirrhotic patients exceed willingness-to-pay thresholds commonly cited in the United States.

Najafzadeh, 2015

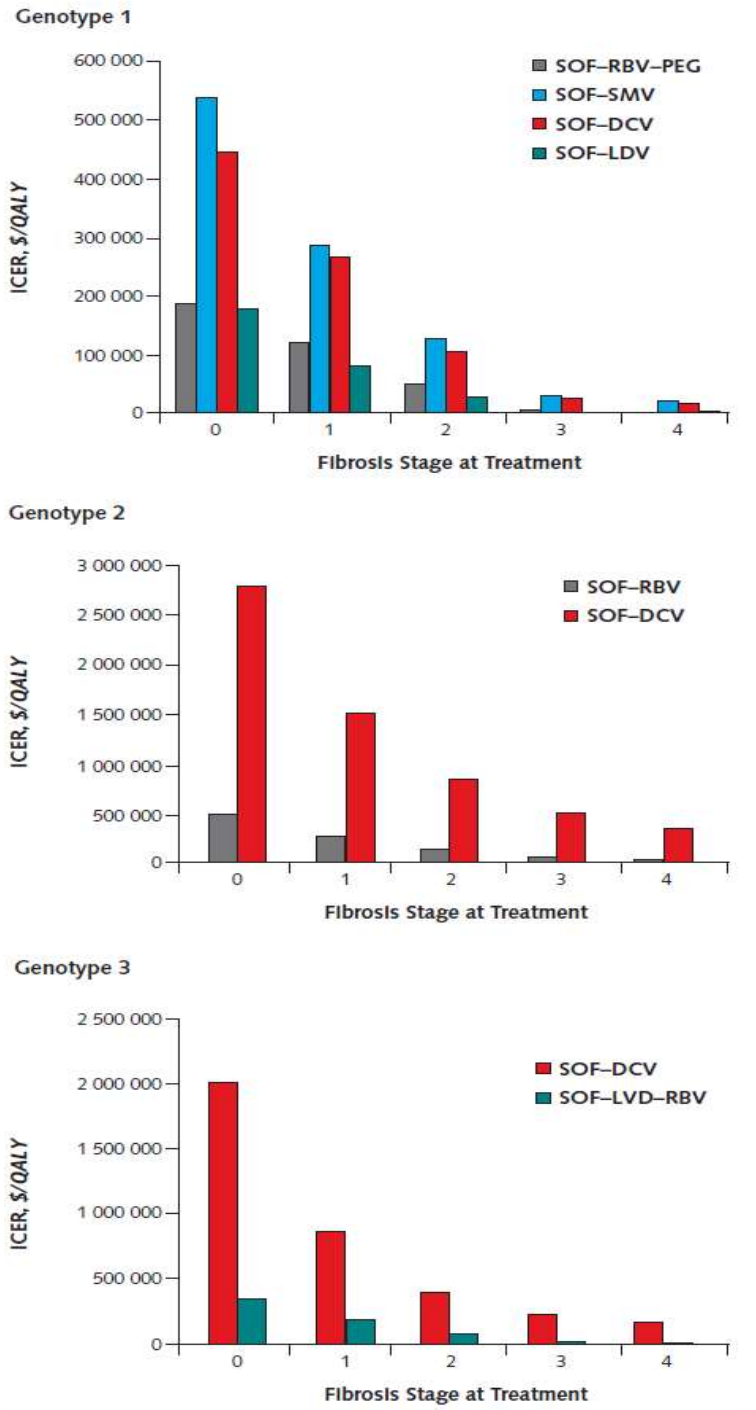
1. Population: Treatment-naive patients infected with chronic HCV genotype 1, 2, or 3.
2. Intervention: *Usual care* (boceprevir–ribavirin–pegylated interferon [PEG]) was compared with sofosbuvir–ribavirin–PEG and 3 PEG-free regimens: sofosbuvir–simeprevir, sofosbuvir–daclatasvir, and sofosbuvir–ledipasvir. For genotypes 2 and 3, *usual care* (ribavirin–PEG) was compared with sofosbuvir–ribavirin, sofosbuvir– daclatasvir, and sofosbuvir–ledipasvir–ribavirin (genotype 3 only).

3. **Results of Base-Case Analysis:** For genotype 1, sofosbuvir–ledipasvir was cost-effective for genotype 1 and cost $12 825 more per QALY than usual care. For genotype 2, sofosbuvir–ribavirin and sofosbuvir–daclatasvir cost $110 000 and $691 000 per QALY, respectively. For genotype 3, sofosbuvir–ledipasvir–ribavirin cost $73 000 per QALY, sofosbuvir–ribavirin was more costly and less effective than usual care, and sofosbuvir–daclatasvir cost more than $396 000 per QALY at assumed prices.

4. **Results of Sensitivity Analysis:** Sofosbuvir–ledipasvir was the optimal strategy in most simulations for genotype 1 and would be cost-saving if sofosbuvir cost less than $5500 per week (for a 12 week treatment course). For genotype 2, sofosbuvir–ribavirin–PEG would be cost-saving if sofosbuvir cost less than $2250 per week. For genotype 3, sofosbuvir– ledipasvir–ribavirin would be cost-saving if sofosbuvir cost less than $1500 per week.

5. Staff conclusions: because the “usual care” comparison for genotype 1 was comparing one DAA to another (that has been withdrawn from the market) the genotype 1 conclusions are not relevant to our question. Sofosbuvir treatment regimens for treatment-naïve patients with genotypes 2 and 3 appears not to be cost-effective.

Appendix Figure 3. ICERs as a function of baseline fibrosis stage, with results of a 1-way sensitivity analysis for genotypes 1 (*top*), 2 (*middle*), and 3 (*bottom*).



Usual care for genotype 1 consisted of response-guided triple therapy using boceprevir–RBV–PEG for 28 to 48 wk. Usual care for genotypes 2 and 3 consisted of dual therapy with ribavirin-PEG for 24 wk. DCV = daclatasvir; ICER = incremental cost-effectiveness ratio; LDV = ledipasvir; PEG = pegylated interferon; QALY = quality-adjusted life-year; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir.

Rein, 2015 Article not included due to length; available online

Population and assumptions: For genotype 1 – comparison pegylated interferon and ribavirin (PR), and a protease inhibitor for HCV genotype (G) 1 and PR alone for G2/3, treatment with PR and sofosbuvir (PRS) for G1/4 and treatment with sofosbuvir and ribavirin (SR) for G2/3 increased QALYs by 555 226, reduced deaths by 80 682, and increased costs by $26.2 billion at an ICER of $47 304 per QALY gained. As compared to PRS/SR, treating with an all oral regimen of sofosbuvir and simeprevir (SS) for G1/4 and SR for G2/3, increased QALYs by 1 110 451 and reduced deaths by an additional 164 540 at an incremental cost of $80.1 billion and an ICER of $72 169.

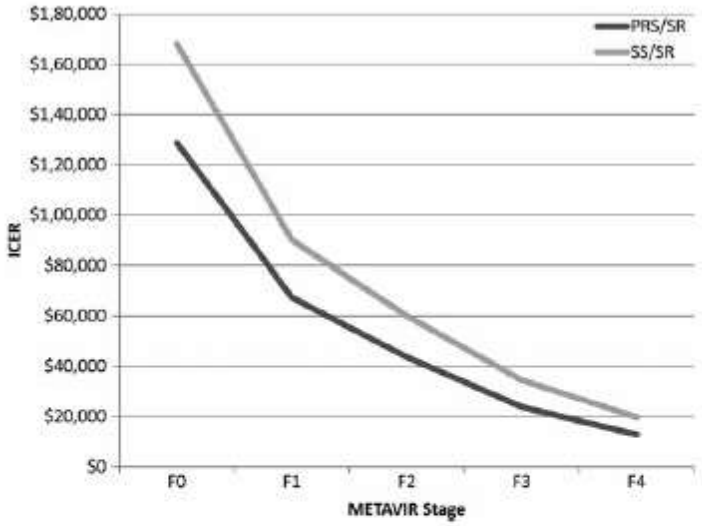


Figure 2. Incremental cost-effectiveness by liver fibrosis score as measured by METAVIR score. Abbreviations: ICER, incremental cost-effectiveness ratio; PRS/SR, pegylated interferon, ribavirin and sofosbuvir for genotypes 1 and 4, and sofosbuvir and ribavirin for genotypes 2 and 3; SS/SR, sofosbuvir and simeprevir for genotypes 1 and 4, and sofosbuvir and ribavirin for genotypes 2 and 3.

Younossi, 2015 Article not included due to length, available online

1. Population/assumptions – oral ledipasvir/sofosbuvir (LDV/SOF), genotype 1

2. One-year costs per SVR, long-term health economic outcomes and long-term health outcomes at different stages of liver fibrosis are presented. Overall, treating patients at an earlier stage of liver fibrosis resulted in lower costs per SVR. Total costs per SVR of LDV/SOF in patients with METAVIR fibrosis score F0–

F1, F2 and F3–F4 were $82 152, $82 399 and $90 878, respectively. Treating patients with METAVIR fibrosis score F0–F1 and F2 with LDV/SOF resulted in a reduction in cost of $8479 and $8726 per SVR, respectively, compared with treating those with score F3–F4 (cost of $90 878 per SVR), a cost reduction of between 9% and 10% per SVR. Treating patients with LDV/SOF resulted in a 66% reduction of overall liver-disease-related complications when patients were treated METAVIR fibrosis score F2 compared with score F3–F4, and by 82% when patients were treated at score F0–F1 compared with score F3–F4.

3. Funded by Gilead, authors with significant conflicts

4. Staff assessment: cost per SVR is not really a standard formula. Authors have many conflicts of interest.

Leidner, 2016

1. Population/assumptions – examined a presumed decrease in non-hepatic mortality by 43%

2. Results: Comparing immediate treatment versus delayed treatment, when we included a 44% reduction in nonhepatic mortality following successful HCV treatment, the incremental cost per quality-adjusted life year (QALY) gained by HCV treatment fell by 76% (from $314,100 to $76,900) for patients with no fibrosis and by 43% (from $62,500 to $35,800) for patients with moderate fibrosis. Comparing immediate treatment versus nontreatment, assuming a 44% reduction in non-hepatic mortality following successful HCV treatment, the incremental cost per QALY gained by HCV treatment fell by 64% (from $186,700 to $67,300) for patients with no fibrosis and by 27% (from $35,000 to $25,500) for patients with moderate fibrosis.

3. Staff assessment – they propose that most cost-effectiveness analyses looking at treatment of chronic hepatitis C underestimate the benefit because they do not include the outcome of a significant decrease in non-hepatic mortality through achieving SVR; their estimates require significant extrapolation and seem to underestimate the effect of confounding.

BUDGET IMPACT

At a national level, some of the cost-effectiveness analyses suggested that treating half the US population with genotype 1 would cost $53 billion, and another estimate is $65 billion for all eligible patients.

OHA budget performed an analysis of the estimated cost of treatment for OHP assuming 100 percent of the eligible F2 population would receive treatment. While treatments vary by patient characteristics, Hepatitis C genotype, and the drug used; the average cost of treatment is $36,247 net of rebates. Cost perspectives to individual CCOs or for individual patients will be different.

OHA budget determined that expanding coverage to F2 would cause serious budget impacts for Prioritized List funding. In order for the funding of the covered services of the Prioritized List to be maintained, OHA has requested additional funds directed toward hepatitis C treatment. Therefore, the Governor's budget requests $32 million in state funds to expand treatment for hepatitis C.

Treatment of F0 and F1 would cause additional issues with the budget, but that additional amount has not been asked for.

HERC Staff summary

Length of time in fibrosis stage

There are a number of longitudinal cohort studies that demonstrate that the risk of progression to decompensated cirrhosis, development of hepatocellular carcinoma, and death are highly associated with the stage of liver fibrosis. Lower stages F0, F1, and F2 are associated with much less risk (one-fourth to one-half the risk) than the higher stages, F3 and F4, over a period of years. From the data on progression, one can argue that prioritizing treatment at higher stages of fibrosis ensures that those most likely to progress to the long-term complications, would have the greatest opportunity to benefit. Some of the studies suggest a natural cutoff between F2 and F3 in terms of worse outcomes. Others show curvilinear increases in risk associated with increasing levels of fibrosis where a cutoff could be argued for a lower fibrosis stage.

The answer to the question of whether it is relatively safe to delay treatment in earlier fibrosis stages appears to be yes. Given that F3 and F4 clearly have worse outcomes than F0-2 and the goal would be to prevent those worse outcomes, expanding the treatment to F2 would ensure that treatment and potentially cure occurs before a patient has transitioned into the fibrosis stages with worse outcomes (i.e. F3 and above). Additionally, there is the possibility that patients who have F3 fibrosis may be misclassified as F2. Again, expanding the treatment to the F2 population would also allow for assurance that all with higher levels of fibrosis would be eligible for treatment.

Harms of DAAs

- No evidence is available on the long-term harms of DAAs
- Short-term harms are largely milder than historical regimens
- Serious adverse events such as reactivation of hepatitis B and accelerated decompensation and death are rare but require monitoring and ongoing caution

Cost-effectiveness analysis summary

- The cost-effectiveness of treatment with DAAs lessens with lower fibrosis stages. Treatment of F0 does not appear to be cost-effective, and treatment of F1 is unlikely to be. Treatment of higher fibrosis stages is likely to be cost-effective. Cost-effectiveness appears to worsen with older age, genotypes 2 and 3, and treatment naiveté.
- Awaiting additional MED report summarizing cost-effectiveness issues

Budget impact

While treating a portion of the chronic hepatitis C population will be cost-effective, the sheer cost of the medications and the prevalence of the condition, creates a significant budget impact.

For OHP, there would be a significant budgetary impact for expanding coverage of hepatitis C. This impact could affect the ability to afford covering all services in the

funded portion of the Prioritized List, or other state spending. As such, additional funds are necessary to expand coverage to include F2.

HERC Staff Recommendations:

2) Create a new line YYY titled CHRONIC VIRAL HEPATITIS C, FIBROSIS STAGES 2-4, including the following chronic viral hepatitis C and standard medical therapy codes (removed from Line 203), with scoring as suggested below:

B18.2	Chronic viral hepatitis C
B19.20	Unspecified viral hepatitis C without hepatic coma
B19.21	Unspecified viral hepatitis C with hepatic coma

Proposed scoring (scoring for Line 203 in parentheses):
Category: 6 (6)
Healthy Life: 7 (7)
Pain/suffering: 2 (2)
Population effects: **3 (5)**
Vulnerable populations: **5 (4)**
Tertiary prevention: 3 (3)
Effectiveness: **4 (2)**
Need for service: 1 (1)
Cost: **1 (2)**
Total score: 3200 (1680)
Rank: 35 (~**Line 203**)

3) Create a new line YYY titled CHRONIC VIRAL HEPATITIS C, FIBROSIS STAGES 0 AND 1, including the following chronic hepatitis C (excluding hepatic coma) and standard medical therapy codes, with scoring as suggested below:

B18.2	Chronic viral hepatitis C
B19.20	Unspecified viral hepatitis C without hepatic coma

Proposed scoring:
Category: 7
Healthy Life: 2
Pain/suffering: 1
Population effects: 3
Vulnerable populations: 4
Tertiary prevention: 1
Effectiveness: 4
Need for service: 0.1
Cost: 1
Total score: 88

Rank: **~Line 535**

4) Review scoring of remaining codes on Line 203 and rename CHRONIC HEPATITIS, VIRAL HEPATITIS EXCLUDING CHRONIC VIRAL HEPATITIS C

Category: 6
Healthy Life: 7
Pain/suffering: 2
Population effects: 5
Vulnerable populations: 4
Tertiary prevention: 3
Effectiveness: 2
Need for service: 1
Cost: 2
Total score: 1680
Rank: 203

5) Discuss adoption of a new guideline note

GUIDELINE NOTE XXX CHRONIC VIRAL HEPATITIS C TREATMENT
Lines YYY, ZZZ
For chronic viral hepatitis C, pharmacologic treatment is only included on Line YYY for fibrosis stages F2-4, otherwise pharmacologic treatment for fibrosis stages F0-1 (or unspecified fibrosis level) is included on Line ZZZ.

Fibrosis stage is to be determined by liver biopsy, clear clinical indications of cirrhosis, or by non-invasive diagnostic testing for liver fibrosis per Guideline Note 76.

6) Discuss whether the guideline note should specifically include moderate-severe extrahepatic manifestations of hepatitis C or whether this could potentially simply be addressed through the comorbidity rule. If they are to be specifically listed out in the guideline note, consider adopting those listed extrahepatic manifestations set forth by the P&T committee. If a patient has lymphoma, HIV, or is post-transplant, this seems like it could be addressed through the comorbidity rule.

Select patients with F0-1 are also included on Line YYY including patients:
1. With one or more of the following documented extrahepatic manifestations:
    a. Type 2 or 3 cryoglobulinemia with end organ manifestations (i.e. leukocytoclastic vasculitis)
    b. Proteinuria, nephrotic syndrome or membranoproliferative glomerulonephritis
    c. Porphyria cutanea tarda

OR

2. Who are either:
    a. Listed for transplant and it is essential to prevent recurrent hepatitis C infection post-transplant; or
    b. Post solid organ transplant

7) Modify GUIDELINE NOTE 76, DIAGNOSTIC TESTING FOR LIVER FIBROSIS TO GUIDE TREATMENT OF HEPATITIS C IN NON-CIRRHOTIC PATIENTS to refer to the new chronic hepatitis C lines YYY, ZZZ
8) Discuss whether to further pursue additional restrictions on the use of pharmacologic treatment in populations that may be less cost-effective, such as in treatment naïve patients with genotypes 2 and 3.
    a. Await upcoming MED report on cost-effectiveness
    b. Staff could work with P&T if this level of guideline is intended and bring it back for March

Hepatitis C Direct-Acting Antivirals

Goals:

- Approve use of cost-effective treatments supported by the medical evidence.
- Provide consistent patient evaluations across all hepatitis C treatments.
- Ensure appropriate patient selection based on disease severity, genotype, and patient comorbidities.

Length of Authorization:

- 8-12 weeks

Requires PA:

- All direct-acting antivirals for treatment of chronic Hepatitis C

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of chronic Hepatitis C infection?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is expected survival from non-HCV-associated morbidities more than 5 years?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Has all of the following pre-treatment testing been performed: a. Genotype testing in past 3 years; b. Baseline HCV RNA level in past 6 months; c. Current HIV status of patient; d. Pregnancy test in past 30 days for a woman of child-bearing age; and e. History of previous HCV treatment and outcome? Note: Direct-acting antiviral agents can re-activate hepatitis B in some patients. Please screen before treatment and monitor carefully during and after treatment for flare-up of hepatitis.	**Yes:** Record results of each test and go to #5	**No**: Pass to RPh. Request updated testing.

Approval Criteria		
5. Has the patient failed treatment with <u>any</u> of the following HCV NS5A inhibitors: a. Daclatasvir plus sofosubvir; b. Ledipasvir/sofosbuvir; c. Paritaprevir/ritonavir/ombitasvir plus dasabuvir; d. Elbasvir/grazoprevir; <u>or</u> e. sofosbuvir/velpatasvir)? <u>Note</u>: Patients who failed treatment with sofosbuvir +/- ribavirin or pegylated interferon can be retreated (see table below).	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: If urgent retreatment is needed, resistance testing must be done to indicate susceptibility to prescribed regimen. Refer to medical director for review.	**No:** Go to #6
6. Which regimen is requested?	Document and go to #7	
7. Is the regimen prescribed by, or in consultation with, a hepatologist, gastroenterologist, or infectious disease specialist with experience in treatment of Hepatitis C?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness. Forward to DMAP for further manual review to determine appropriateness of prescriber.
8. Does the patient have: a. A biopsy, imaging test (transient elastography [FibroScan®], acoustic radiation force impulse imaging [ARFI], or shear wave elastography [SWE]) to indicate advanced fibrosis (METAVIR F3) or cirrhosis (METAVIR F4); <u>or</u> b. Clinical, radiologic or laboratory evidence of complications of advanced cirrhosis (ascites, portal hypertension, hepatic encephalopathy, hepatocellular carcinoma)**?**	**Yes:** Go to #12 Note: Other imaging and blood tests are not recommended based on insufficient evidence for high sensitivity and specificity compared to a liver biopsy	**No:** Go to #9

Approval Criteria		
9. Does the patient have HIV coinfection AND: A biopsy, imaging test (transient elastography [FibroScan®], acoustic radiation force impulse imaging [ARFI], or shear wave elastography [SWE]), or serum test if the above are not available (enhanced liver fibrosis [ELF]; Fibrometer; FIBROSpect II) to indicate fibrosis (METAVIR F2) AND the patient is under treatment by a specialist with experience in HIV?	**Yes:** Go to #12 Note: Other imaging and blood tests are not recommended based on insufficient evidence for high sensitivity and specificity compared to a liver biopsy	**No:** Go to #10
10. Does the patient have one of the following extrahepatic manifestations of Hepatitis C (with documentation from a relevant specialist that their condition is related to HCV)? a. Type 2 or 3 cryoglobulinemia with end-organ manifestations (i.e., leukocytoclastic vasculitis); or b. Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis; or c. Porphyria cutanea tarda	**Yes:** Go to #12	**No:** Go to #11
11. Is the patient in one of the following transplant settings: a. Listed for transplant and it is essential to prevent recurrent hepatitis C infection post-transplant; or b. Post solid organ transplant?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness.
12. In the previous 6 months: a. Has the patient actively abused alcohol (>14 drinks per week for men or >7 drinks per week for women or binge alcohol use (>4 drinks per occasion at least once a month); or b. Has the patient been diagnosed with a substance use disorder; or c. Is the prescriber aware of current alcohol abuse or illicit injectable drug use?	**Yes:** Go to #13	**No:** Go to #14
13. Is the patient enrolled in a treatment program under the care of an addiction/substance use treatment specialist?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
14. Will the patient and provider comply with all case management interventions and adhere to monitoring requirements required by the Oregon Health Authority, including measuring and reporting of a post-treatment viral load?	**Yes**: Go to #15	**No:** Pass to RPh. Deny; medical appropriateness.
15. Is the prescribed drug: a. Elbasvir/grazoprevir for GT 1a infection; or b. Daclatasvir + sofosbuvir for GT 3 infection?	**Yes**: Go to #16	**No:** Go to #17
16. Has the patient had a baseline NS5a resistance test showing a resistant variant to one of the agents in #16?	**Yes:** Pass to RPh; deny for appropriateness	**No:** Go to #17
17. Is the prescribed drug regimen a recommended regimen based on the patient's genotype and cirrhosis status (see Table 1)?	**Yes:** Approve for 8-12 weeks based on duration of treatment indicated for approved regimen (Table 1).	**No:** Pass to RPh. Deny; medical appropriateness.

Table 1: Recommended Treatment Regimens for Chronic Hepatitis C.

Genotype	Cirrhosis Status	Approved Regimen^	Duration of Treatment
Genotype 1			
Treatment-naïve	Non-cirrhotic	• EBR/GZR • LDV/SOF	12 weeks except if LDV/SOF and *HCV RNA < 6 million IU/mL, give for 8 weeks*
	Compensated Cirrhosis	• EBR/GZR • LDV/SOF	12 weeks
	Decompensated Cirrhosis	• LDV/SOF + RBV	12 weeks
Treatment-experienced*	Non-cirrhotic	• EBR/GZR • LDV/SOF +/- RBV±	12 weeks
	Compensated Cirrhosis	• EBR/GZR +/- RBV± • LDV/SOF + RBV	12 weeks
	Decompensated Cirrhosis	• LDV/SOF + RBV	24 weeks
Genotype 2			
Naïve or	Non-cirrhotic	• SOF/VEL+/- RBV±	12 weeks

Experienced	Compensated Cirrhosis	• SOF/VEL+/- RBV±	12 weeks
	Decompensated Cirrhosis	• SOF/VEL + RBV	12 weeks
Genotype 3			
Naïve or Experienced	Non-cirrhotic	• LDV/SOF + RBV • SOF/VEL	12 weeks
	Compensated Cirrhosis	• SOF/VEL + RBV • DCV/SOF + RBV	12 weeks
	Decompensated Cirrhosis	• SOF/VEL + RBV • DCV/SOF + RBV	12 weeks
Genotype 4			
Naïve	Non-cirrhotic	• EBR/GZR • LDV/SOF	12 weeks
	Compensated Cirrhosis	• EBR/GZR • LDV/SOF	12 weeks
	Decompensated Cirrhosis	• LDV/SOF + RBV	12 weeks
Experienced	Non-cirrhotic	• EBR/GZR +/- RBV • LDV/SOF	12 weeks -16 weeks (patients with prior on-treatment failure while on PEG should be treated with 16 weeks and have RBV added to EBR/GZR regimen)
	Compensated Cirrhosis	• EBR/GZR +/- RBV • LDV/SOF + RBV	12 weeks-16 weeks (patients with prior on-treatment failure while on PEG should be treated with 16 weeks and have RBV added to EBR/GZR regimen)
	Decompensated Cirrhosis	• LDV/SOF + RBV	12 weeks
Genotypes 5 and 6			
Naïve or Experienced	With or Without Cirrhosis	• LDV/SOF	12 weeks

Abbreviations: DCV = daclatasvir (Daklinza®); EBV/GZR = elbasvir/grazoprevir (Zepatier®) ; LDV/SOF = ledipasvir and sofosbuvir (Harvoni®); PEG = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir (Sovaldi®); SOF/VEL = sofosbuvir/velpatasvir (Epclusa®)

*Treatment-experienced defined as previous treatment with PEG/RBV or SOF/RBV only.

± Weight based ribavirin recommended in whom prior treatment with sofosbuvir and ribavirin has failed

^ Rarely, genotyping assays may indicate the presence of a mixed infection (e.g., genotypes 1a and 2). Treatment data for mixed genotypes with direct-acting antivirals are limited. However, in these cases, a pangenotypic regimen is appropriate.
Ribavirin-containing regimens are absolutely contraindicated in pregnant women and in the male partners of women who are pregnant. Documented use of two forms of birth control in patients and sex partners for whom a ribavirin-containing regimen is chosen is required.
Sofosbuvir-containing regimens should not be used in patients with severe renal impairment (GRF < 30 mL/min) or end stage renal disease requiring dialysis.
Elbasvir/grazoprevir or ombitasvir/paritaprevir/ritonavir + dasubuvir should not be used in patients with moderate to severe hepatic impairment (CTP and C)

P&T/DUR Review: *9/16 (MH); 1/16; 5/15; 3/15; 1/15; 9/14; 1/14*
Implementation: *TBD; 2/12/16; 4/15; 1/15*

Treating Hepatitis C at Liver Fibrosis Stage F2 versus F3

Participant Request

December 2016

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Overview

This report reviews the evidence regarding the association between liver fibrosis stage in patients with chronic hepatitis C (HCV) infection and mortality and liver-related outcomes (e.g., decompensated cirrhosis, hepatocellular carcinoma [HCC], liver transplant). The report summarizes evidence on the differences in clinical outcomes for patients with HCV related to fibrosis stage, specifically Metavir score F2 compared to F3 and F4. The report also summarizes the evidence regarding harms of treatment with the newer direct-acting antiviral agents (DAA) and the influence of DAAs on extrahepatic manifestations of HCV.

Key Findings

- Center researchers did not find any systematic reviews, controlled trials, or comparative observational studies that examined how treating patients with F2 fibrosis versus delaying treatment until Stage F3 or F4 affects clinical outcomes.
- Risk of progression to decompensated cirrhosis, HCC, and death varies greatly by liver fibrosis stage. The one-year and five-year risk of these outcomes in patients with Stage F0 to F2 fibrosis are about one-fourth to one-half as much as the risks for patients with Stage F3 and F4 fibrosis.
- Center researchers found no studies on how newer DAAs affect extrahepatic manifestations of HCV.
- Center researchers found no comparative or cohort studies that reported long-term harms of DAAs. However, case reports suggest that DAAs could cause reactivation of hepatitis B (HBV) in patients who have HCV/HBV coinfections; these reports resulted in a U.S. Food and Drug Administration (FDA) black box warning. Cases have been reported of accelerated decompensation and death in patients with moderate to severely decompensated cirrhosis who have taken DAAs, and a drug approval study was stopped because of cardiotoxicity from a DAA with a pharmacological structure similar to sofosbuvir.
- Only one recent systematic review examined the harms or adverse events of the new DAAs and focused on the DAAs that would have the most influence on quality of life and resource use: rash, anemia, and depression. Indirect comparisons from a network meta-analysis found that in general, fewer patients who took DAAs had rashes, anemia, and depression compared to interferon-based regimens. Other common adverse events were fatigue, headaches, and insomnia, but these were generally mild to moderate and caused few people to discontinue treatment.

Background

HCV affects approximately 2.7 million people in the U.S. (Denniston et al., 2014), but estimates are as high as 5.2 million people (Chak, Talal, Sherman, Schiff, & Saab, 2011; Edlin, Eckhardt, Shu, Holmberg, & Swan, 2015). Surveillance studies suggest that 47,435 Oregonians might have chronic HCV infections (Oregon Public Health Division, 2015). Each year from 2009 to 2013, the Oregon Public Health Division received an average of 5,087 reports of HCV (Oregon Public Health Division, 2015). Although the rate of laboratory-reported HCV infections has declined in Oregon since 2009, it is increasing in people younger than 30 years old (Oregon Public Health Division, 2015). In people with acute HCV infections, about 50% are younger than 30 years, 56% are male, and 64% inject drugs (Oregon Public Health Division, 2015). The Centers for Disease Control and Prevention (CDC) identified people who inject drugs as a high-risk population and has growing concerns about HCV transmission in this population (Centers for Disease Control and Prevention Division of Viral Hepatitis, 2015).

Several other populations are known to have a higher prevalence of chronic HCV. Among people covered by Medicaid, the prevalence of HCV infection is two to seven times that of commercially insured populations (Levin, 2013; Milliman, 2015). African Americans and Native Americans have rates of HCV that are twice that of Caucasians, and 16% to 41% of incarcerated people reportedly have HCV, including an estimated 30% of incarcerated people in Oregon (Oregon Public Health Division, 2015).

Rate of Fibrosis Progression

Fibrosis of the liver is an important predictor of clinical outcomes from HCV (Chou et al., 2013; Vergniol et al., 2014). The highest rates of complications occur in patients with advanced fibrosis and cirrhosis. Clinicians most commonly use Metavir fibrosis scores (Bedossa & Poynard, 1996) to determine the stage of liver fibrosis (Chou et al., 2013). Metavir scores range from F0 (no fibrosis) to F4 (cirrhosis). A Metavir score of F0 to F1 indicates minimal or no fibrosis, F2 to F4 indicates increasing levels of fibrosis, and F4 indicates cirrhosis (Bedossa & Poynard, 1996; Chou et al., 2013).

Liver fibrosis from HCV tends to progress slowly (Lok et al., 2009). In a 20- to 30-year period, 5% to 20% of people with HCV will develop cirrhosis, and 1% to 5% will die from cirrhosis or liver cancer (Centers for Disease Control and Prevention, 2014). These estimates could be high because previous observational studies have been conducted in populations with other known risk factors. Therefore, these estimates may be confounded by conditions and behaviors known to increase the risk of progression to serious liver-related outcomes (Butt, Yan, Lo Re, Iii, & et al., 2015; Goodgame, Shaheen, Galanko, & El-Serag, 2003; Koretz, Lin, Ioannidis, & Lenzer, 2015) including alcohol use, smoking cigarettes or marijuana, obesity, and coinfection with hepatitis B or HIV (Feld & Liang, 2006; Hezode et al., 2005; Mallat, Hezode, & Lotersztajn, 2008; Missiha, Ostrowski, & Heathcote, 2008).

Recently, Butt et al. (2015) published a good-quality longitudinal cohort study using a national Department of Veterans Affairs database to determine the rate of fibrosis progression and factors associated with progression. They identified 1,840 patients who were HCV negative and became HCV positive (an inception cohort) and matched them to 1,840 HCV-negative patients according to age, gender, and race. Using the FIB-4 index, which uses age and routinely collected laboratory data (aspartate aminotransferase, alanine aminotransferase, and platelet count), they assessed liver fibrosis progression. The authors gathered data on patients until they had a liver-related outcome, died, or started HCV treatment.

HCV-positive patients were younger (median age, 49 vs. 52, respectively, $p < 0.001$) and more likely to have alcohol (53% vs. 31%, $p < 0.001$) and drug (58% vs. 24%, $p < 0.001$) use disorders. In the HCV-positive group, progression of fibrosis started early, but tapered off after five years. After 10 years, more HCV-positive patients than HCV-negative patients had cirrhosis (18.4% vs. 6.1%, $p < 0.001$). Approximately nine years after cirrhosis developed, decompensated cirrhosis was uncommon, but occurred more often in HCV-positive patients (1.79% vs. 0.33%, $p < 0.001$). Age, racial background (Caucasian), hypertension, anemia, and history of alcohol abuse or dependence were associated with developing cirrhosis, but only age remained significantly associated with cirrhosis after patients with alcohol abuse and dependence at baseline were removed from the study (Butt et al., 2015).

Because little is known about how newer DAA regimens affect long-term liver-related outcomes, the question arises of when to treat people with HCV to decrease their risk of these outcomes (Konerman, Yapali, & Lok, 2014; Koretz et al., 2015). Identifying people at greater risk of progression of liver fibrosis and clinical outcomes is a priority (National Academies of Sciences, Engineering, & and Medicine, 2016) and could help determine who should receive treatment sooner and in whom treatment can be safely delayed.

Objective

The main objective of this report is to identify evidence on how delaying treatment of chronic HCV infection until patients have advanced fibrosis (Stages F3 or F4) versus treating patients at Stage F2 affects outcomes at the individual and population levels. Secondary objectives are to summarize the evidence on the harms of treatment with newer DAAs and treatment outcomes related to extrahepatic manifestation of HCV (e.g., mixed cryoglobulinemia, vasculitis lymphoproliferative disorders, glomerulonephritis, inflammatory polyarthropathies).

Methods

Center researchers searched PubMed Health and OVID Medline for systematic reviews, technology assessments, and meta-analyses of studies assessing Metavir fibrosis score as a predictor of clinical outcomes for HCV infection. The search was limited to references published in English within the last two years (January 2014 to December 2016). For this report, we updated a previous search conducted for the report *Association of Metavir Scores and Clinical*

Outcomes to include studies published from January 2016 to the present for the main objective, and then we performed separate searches of PubMed Health and OVID Medline for systematic reviews, technology assessments, and meta-analyses of studies published in the past two years addressing the harms or adverse events from DAAs and the effectiveness of DAAs for outcomes related to extrahepatic manifestation of HCV. (See Appendix A for the search strategies). Center researchers also searched for related studies in Medline using medical subject headings (MeSH) terms related to studies selected from the initial search. For the questions about harms and extrahepatic manifestations of HCV, researchers also reviewed studies cited in the AASLD/IDSA guidelines (American Association for the Study of Liver Diseases and the Infectious Diseases Society of America, 2016).

Findings

Key Question 1: What are the consequences of delaying treatment of HCV until patients have F3 liver fibrosis compared to treating at the F2 stage?

Many studies have identified factors associated with the progression of liver disease in patients with HCV, but few have used a longitudinal cohort design to assess liver fibrosis stage as a predictor of clinical outcomes. The report by Gerrity, Carson, and Harrod (2016) has information pertinent to Key Question 1 and will be summarized here (for more information, please see the report).

For the August 2016 report, Center researchers identified one systematic review (Konerman et al., 2014) and two longitudinal studies (Huang et al., 2015; Zeremski et al., 2016) published after the search date of the systematic review. Konerman et al. (2014) identified 29 studies from 20 cohorts that included 5,817 patients with HCV and no coinfections. All 29 studies used longitudinal study designs and involved mostly untreated men in their thirties to fifties who had paired liver biopsies. The incidence of fibrosis progression and clinical outcomes varied across studies. The incidence of fibrosis progression on follow-up biopsy ranged from 21% to 61% in a follow-up period of 2.5 to 10 years using an increase of more than one Metavir fibrosis stage as the criterion for progression. Progression from compensated to decompensated cirrhosis ranged from 13% to 40% during a range of 2.3 to 14.3 years, and overall mortality ranged from 8% to 47% in 3.9 to 14.4 years. None of the included studies assessed the association between Metavir fibrosis stage and clinical outcomes, except as noted.

Risk of progression to decompensated cirrhosis and death vary greatly by liver fibrosis stage.

The two additional studies (Huang et al., 2015; Zeremski et al., 2016) were longitudinal studies from single institutions. Huang et al. (2015) identified 1,033 patients with HCV who had liver biopsies done between 1992 and 2012 and linked biopsy data with clinical outcomes data from

statewide data systems in Australia. For the 880 patients with complete data, the Metavir fibrosis stages at the time of first biopsy are listed in Table 1, along with estimated survival probabilities by stage.

Table 1. Estimates of Survival by Metavir Score

Metavir score	Fibrosis stage on initial liver biopsy N (%)	18-year survival probability (95% CI)	15-year HCC-free survival (95% CI)	15-year hepatic decompensation-free survival (95% CI)
F0	173 (20)	99% (96–100%)	100%	100%
F1	383 (44)	96% (91–98%)	99% (98–100%)	96% (93–98%)
F2	124 (14)	94% (83–98%)	98% (92–100%)	94% (86–97%)
F3	80 (9)	77% (51–91%)	78% (52–91%)*	86% (70–94%)*
F4	73 (8)	40% (23–57%)**	78% (62–88%)†	58% (44–70%)†

* 18-year HCC-related and hepatic decompensation-free survival probability

** 15-year survival probability

† 10-year survival probability

Most patients (78%) had fibrosis stages F0 to F2 at the time of initial liver biopsy. Liver-related survival probability was not significantly different between patients with F0, F1, or F2 fibrosis ($p = 0.163$). Patients with F0–F2 fibrosis also had higher HCC-free and hepatic decompensation-free survival probability (Table 1). In contrast, survival probability was significantly lower for patients with F3 and F4 fibrosis: The age-adjusted hazard ratio for F3 (versus F0–F2) was 4.24 (95% CI, 1.6 to 10.9) and for F4 was 23.0 (95% CI, 10.7 to 49.6).

In the second study, Zeremski et al. (2016) identified 378 patients with HCV from electronic records at a New York City hospital. To be included in the study, patients had to have at least two liver biopsies between 1997 and 2013. Patients who had cirrhosis on first biopsy, responded to HCV treatment, or had a liver transplant were excluded. For the remaining 248 patients with two or more biopsies, the following is the percentage of patients according to fibrosis stage:

- F0: 12% of patients
- F1: 32% of patients
- F2: 39% of patients
- F3: 16% of patients

Between the first and last biopsy, 217 (57%) patients had progressed at least one fibrosis stage; 61 (16%) had progressed at least two fibrosis stages. Twenty-two (11%) patients progressed to cirrhosis during a mean of 7.6 years (standard deviation 3.6 years) from first biopsy. The estimated time spent in a fibrosis stage was shortest for fibrosis Stage 0 (2.55 years; 95% CI, 1.61

to 4.04 years) and longest for Stage F2 (18.4 years; 95% CI, 11.5 to 29.4 years). Higher alanine transaminase (> 200 U/L) was associated with progression from fibrosis Stage F2 to F3 (hazard ratio 1.16; 95% CI, 1.06 to 1.28).

Additional Studies

For this report, Center researchers identified two additional studies that described the probability of progression of liver disease. The first study by Thein, Yi, Dore, and Krahn (2008) is a systematic review of prognostic studies published between 1990 and 2007. The authors included 111 studies (33,121 patients) in their models to estimate progression rates for liver fibrosis: 100 studies were cross-sectional with information about estimated time of first infection; 11 studies were retrospective cohort studies (patients were identified at the time of acute HCV infection or exposure from past records and were contacted for follow-up or received follow-up care); 97 studies were from clinical settings (including 79 from liver clinics); and 14 studies were from non-clinical settings (e.g., screening programs) (Thein et al., 2008). None of the included studies used a prospective cohort design, and it was unclear whether patients in the studies received treatment for HCV. Most of the patients in these studies were male (62%) and had a mean estimated duration of HCV infection of 17.5 years. Injection drug use (41%) and blood product transfusion (31%) were the most common risk factors for HCV infection. Almost all (95%) of the patients had liver biopsies to assess liver fibrosis (Thein et al., 2008).

Thein et al. (2008) used the Markov maximum likelihood estimation method and data from the included studies to develop annual stage-specific transition probabilities (Table 2), such as the probability of moving from Stage F0 to F1. Transition rates were not linear. The probability of transitioning from Stage F0 to F1 was higher than for Stage F1 to F2. The highest probability of transitioning to the next stage was from Stage F2 to F3 (annual mean transition probability 0.12; 95% CI, 0.109 to 0.133

Table 2. Estimated Annual Mean Transition Probabilities by Fibrosis Stage

Transition of Metavir Fibrosis Stage	Annual Mean Transition Probability (95% CI)
F0 -> F1	0.117 (0.104 to 0.13)
F1 -> F2	0.085 (0.075 to 0.096)
F2 -> F3	0.12 (0.109 to 0.133)
F3 -> F4	0.116 (0.104 to 0.129)

Note. 95% CI indicates 95% confidence interval.

In a 20-year period, the estimated probability of developing cirrhosis was 16% (95% CI, 14% to 19%) overall, but varied by type of study and patient characteristics: 18% (15% to 21%) for cross-sectional studies, 7% (4% to 12%) for retrospective cohort studies, 15% (13% to 18%) for studies published in 2000 and later, 33% (20% to 58%) for studies published before 2000, and 41% (36% to 45%) for patients who acquired HCV infection when they were older than 30 (about two to three times higher than if HCV was acquired before age 30) (Thein et al., 2008). The authors developed a regression model that could predict stage-specific progression rates and risk of cirrhosis for groups of patients with specific characteristics based on covariates in the model (Thein et al., 2008). However, Center researchers did not find subsequent studies validating this model.

Xu et al. (2016) conducted a cohort study of patients with HCV mono-infection who had liver biopsies done between 2001 and 2012. Patients were identified from records at four large integrated health systems in the U.S. Most of the 2,799 patients were male (58.9%) and non-Hispanic white (66.9%) and had a mean age of 50.7 years at the time of liver biopsy. Approximately 40% of patients had F0 or F1 fibrosis and 30% had F2 fibrosis. During approximately five years of observation, 54% were prescribed treatment with older interferon-based regimens, 24% had two or more courses prescribed, and 910 patients cleared their HCV infection after treatment, at which time their study observation period ended. The probability of progression to liver-related outcomes and all-cause mortality in the one-year and five-year follow-up periods is displayed in Table 3.

Table 3. One- and Five-Year Probabilities of Clinical Outcomes by Fibrosis Stage

Metavir Fibrosis Stage* N (%)	Follow-up Period	Hepatic Decompensation % (95% CI)	HCC % (95% CI)	Liver Transplant % (95% CI)	All-cause Mortality % (95% CI)
F0-F1 1033 (40%)	1 year	0.4 (0.2 to 1.1)	0	0.1 (0.01 to 0.6)	1.5 (0.9 to 2.4)
	5 years	2.3 (1.3 to 3.8)	0	0.3 (0.06 to 1.1)	6.8 (5.0 to 9.0)
F2 849 (30%)	1 year	1.1 (0.5 to 2.2)	0.1 (0.01 to 0.7)	0.1 (0.01 to 0.8)	1.7 (0.9 to 2.8)
	5 years	3.5 (2.1 to 5.5)	1.2 (0.4 to 2.8)	0.4 (0.1 to 1.4)	6.9 (4.7 to 9.5)
F3 509 (18%)	1 year	4.0 (2.4 to 6.3)	1.7 (0.7 to 3.3)	0.2 (0.01 to 1.1)	4.8 (3.0 to 7.3)
	5 years	18.6 (13.5 to 24.4)	3.3 (1.6 to 6.2)	2.4 (0.7 to 6.2)	13.7 (9.4 to 18.9)
F4 408 (14%)	1 year	13.4 (10.0 to 17.3)	4.8 (2.8 to 7.4)	1.6 (0.6 to 3.4)	8.0 (5.4 to 11.3)
	5-year	33.6 (27.7 to 39.5)	11.7 (8.0 to 16.1)	6.5 (3.8 to 10.2)	31.5 (25.6 to 38.2)

Note. HCC indicates hepatocellular carcinoma. 95% CI indicates 95% confidence interval.
**Metavir fibrosis stage is based on first liver biopsy after the diagnosis of HCV.*
Adapted from Xu et al. (2016).

Overall, the probability of liver-related clinical outcomes and mortality doubled for each increase in stage for the one-year and five-year follow-up periods. The five-year probability of decompensated cirrhosis ranged from 2.3% for patients with Stage F0–F1 fibrosis to 33.6% for patients with Stage F4 fibrosis, and all-cause mortality ranged from 6.8% to 31.5%, respectively (Xu et al., 2016). For patients with Stage F2 fibrosis, 3.5% developed decompensated cirrhosis, 1.2% developed HCC, 0.4% had a liver transplant, and 6.9% died within the five-year period. There was no difference in probability of liver decompensation for patients with Stage F0–F1 and those with Stage F2 fibrosis ($p = 0.9$) (Xu et al., 2016).

Spontaneous Clearance of HCV

Although studies of HCV infection have indicated that 15% to 25% of people will clear their acute infection (Butt et al., 2015; Centers for Disease Control and Prevention, 2014), Center

researchers found no studies of spontaneous clearance of chronic HCV infection and specifically spontaneous clearance of HCV when patients have Stage F2 liver fibrosis.

Risk of Transmission

Although HCV is difficult to transmit compared to other viruses such as HBV and HIV, several groups of people with chronic HCV are at increased risk of transmitting HCV infection to others: people who inject drugs, incarcerated individuals, and men having sex with men who also have HIV coinfections (Martin, Vickerman, Dore, Hickman 2015). People who inject drugs could account for up to 80% of HCV transmission in high-income countries (Centers for Disease Control and Prevention Division of Viral Hepatitis, 2015; Hellard et al., 2015; Martin, Vickerman, Dore, & Hickman, 2015; Williams, Bell, Kuhnert, & Alter, 2011; Wu et al., 2006). Because of the potential to spread HCV infection, many researchers, guidelines, and the Centers for Disease Control and Prevention have called for increased HCV testing and treatment, in addition to addiction and mental health treatment, for people who inject drugs (American Association for the Study of Liver Diseases and the Infectious Diseases Society of America, 2016; Centers for Disease Control and Prevention Division of Viral Hepatitis, 2015).

Key Question 2: What are the harms associated with the newer direct acting antiviral drugs for HCV?

Center researchers identified one systematic review that examined three important adverse events in terms of their influence on patients' quality of life and health care resource use: rash, anemia, and depression (Canadian Agency for Drugs and Technologies in Health, 2016). In a network meta-analysis, there were direct and indirect comparisons between interferon-based regimens and three DAA regimens:

- Sofosbuvir (SOF)/ledipasvir (LDV)
- Paritaprevir/ritonavir/ombitasvir plus twice daily dosed dasabuvir (PRoD)
- Daclatasvir (DCV)-based regimens

The authors found that all three regimens had lower rates of anemia and rash compared to older interferon-based regimens, but only SOF+LDV had lower rates of depression compared to older regimens (Canadian Agency for Drugs and Technologies in Health, 2016). Across all three adverse events, SOF+LDV had lower rates than PRoD. Other adverse events that were frequently reported across the three treatment regimens included pruritus and fatigue.

The frequency of other, more serious adverse events ranged from 0% to 21% across the studies, and reporting of these events was inadequate for network meta-analysis (Canadian Agency for Drugs and Technologies in Health, 2016). Clinical outcomes (e.g., decompensated cirrhosis, liver transplant, HCC) and all-cause mortality (range 0% to 1%), withdrawal stemming from adverse events (range 0% to 3%), and all-cause withdrawals (range 0% to 46%) were infrequently

reported in the included studies (Canadian Agency for Drugs and Technologies in Health, 2016) (See Table 68 in the citation).

Serious longer-term harms have been reported, but only as case reports. Most notable is the reemergence of HBV after successful treatment of HCV in patients with HBV and HCV coinfection, resulting in an FDA black box warning (U.S. Food and Drug Adminstration, 2016). In addition, in people with moderate to severe decompensated cirrhosis, the new DAAs may accelerate liver decompensation and result in death (American Association for the Study of Liver Diseases and the Infectious Diseases Society of America, 2016). Finally, the evaluation of a DAA with pharmacological characteristics similar to sofosbuvir was stopped because of serious cardiac toxicity and death (Ahmad et al., 2015; Padegimas, Forde, Goldberg, & Birati, 2016).

Although technically not considered an adverse event, the development of NS5A resistance-associated variants stemming from some of the new DAAs could be an important outcome, especially on a population level. Drugs that have been reported to induce resistance-associated variants are daclatasvir, fixed-dose combination pill sofosbuvir/ledipasvir, fixed-dose combination pill paritaprevir/ritonavir/ombitasvir plus twice daily dosed dasabuvir , simeprevir, and elbasvir/grazoprevir. Sofosbuvir has not been significantly associated with the development of resistance-associated variants.

Key Question 3: How does treatment of HCV affect extrahepatic manifestations such as cryoglobulinemia and glomerulonephritis?

Extrahepatic (non-liver) manifestations are common in people with HCV (Ali & Zein, 2005). The following conditions are frequently noted as extrahepatic (non-liver) manifestations of HCV (Ali & Zein, 2005), but this list is not exhaustive:

- Cryoglobulinemia and vasculitis
- Renal disease
- Diabetes
- Thyroid disease
- Vitamin D deficiency
- Erectile dysfunction
- Cholangiocarcinoma
- Parkinson's disease
- Cardiovascular disease
- Severe fatigue

One study using databases from the Department of Veterans Affairs identified all patients with HCV hospitalized between 1992 and 1999 (n = 34,204) and matched them to randomly chosen control patients without HCV (n = 136,816) hospitalized the same year (El-Serag, Hampel, Yeh, & Rabeneck, 2002). The authors searched inpatient and outpatient records for disorders reported

to be associated with HCV infections and examined the association between HCV and these disorders, using multivariate analysis to control for age, gender, ethnicity, and period of military service. HCV was significantly associated with porphyria cutanea tarda (adjusted odds ratio [aOR], 7.2 to 12.1), lichen planus (aOR, 1.8 to 3.1), vitiligo (aOR, 1.1 to 2.1), cryoglobulinemia (aOR, 10.6 to 20.3), membranoproliferative glomerulonephritis (aOR, 10.6 to 20.3), and non-Hodgkins lymphoma (aOR, 1.0 to 1.4). HCV was not associated with thyroiditis, Sjögren's syndrome, Hodgkin's lymphoma, or diabetes.

Center researchers did not identify any systematic reviews or RCTs that assessed extrahepatic manifestations as an outcome of HCV treatment with the newer DAA regimens. According to Shiffman and Benhamou (2015), no studies assessing the effectiveness and tolerability of oral HCV regimens on extrahepatic manifestations of HCV had been published as of 2015, but they expected studies to be published in 2016 on this topic.

Discussion

Center researchers did not find any systematic reviews, controlled trials, or comparative observational studies that examined how treating patients with Stage F2 fibrosis versus delaying treatment until Stage F3 or F4 affects clinical outcomes (e.g., decompensated cirrhosis, HCC, mortality). One systematic review of observational studies, three additional observational studies, and one modeling study provided information about fibrosis progression and, when available, clinical outcomes. However, the included studies have serious limitations because treatment naïve and treatment experienced, primarily with interferon-based regimens, patients were included in many of the studies. In fact, there are few good-quality long-term prognostic studies of HCV (National Academies of Sciences et al., 2016).

Risk of progression to decompensated cirrhosis, HCC, and death vary greatly by liver fibrosis stage. As a rough estimate, given the risk of bias in the studies, the one-year and five-year risk of these outcomes in people with Stage F0 to F2 fibrosis are approximately one-fourth to one-half much as that of those with Stage F3 and F4 fibrosis.

Center researchers searched for studies addressing the harms associated with the newer DAAs and how they affect extrahepatic manifestations of HCV and found the following:

- No studies on how newer DAAs affect extrahepatic manifestations of HCV
- No comparative or cohort studies that reported long-term harms of DAAs

However, case reports suggest that DAAs may cause reactivation of HBV in patients who have HCV/HBV coinfections; these reports have resulted in an FDA black box warning. In addition, there have been case reports of accelerated decompensation and death in patients with moderate to severely decompensated cirrhosis and cardiotoxicity from a DAA that was withdrawn from development, but had a pharmacological structure similar to sofosbuvir.

Only one recent systematic review examined the harms or adverse events of the new DAAs and focused on those that would have the most influence on quality of life and resource use: rash, anemia, and depression. In general, fewer patients taking DAAs had rashes, anemia, and depression compared to patients on interferon-based regimens, based on indirect comparisons from a network meta-analysis. Other common adverse events were fatigue, headaches, and insomnia, but these were generally mild to moderate and few people discontinued treatment.

References

Ahmad, T., Yin, P., Saffitz, J., Pockros, P. J., Lalezari, J., Shiffman, M., ... Hernandez, A. F. (2015). Cardiac dysfunction associated with a nucleotide polymerase inhibitor for treatment of hepatitis C. *Hepatology, 62*(2), 409-416. DOI: 10.1002/hep.27488

Ali, A., & Zein, N. N. (2005). Hepatitis C infection: a systemic disease with extrahepatic manifestations. *Cleveland Clinic Journal of Medicine, 72*(11), 1005-1008, 1010-1004, 1016 passim.

American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. (2016). HCV Guidance: Recommendations for testing, managing, and treating hepatitis C. Retrieved July 15, 2016, Retrieved from http://www.hcvguidelines.org/full-report-view

Bedossa, P., & Poynard, T. (1996). An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. *Hepatology, 24*(2), 289-293. DOI: 10.1002/hep.510240201

Butt, A. A., Yan, P., Lo Re, V., Iii, & et al. (2015). Liver fibrosis progression in hepatitis C virus infection after seroconversion. *JAMA Internal Medicine, 175*(2), 178-185. DOI: 10.1001/jamainternmed.2014.6502

Canadian Agency for Drugs and Technologies in Health. (2016). Drugs for chronic hepatitis C infection: Clinical review. Retrieved from https://www.cadth.ca/sites/default/files/pdf/TR0008_Clinical_Report-en.pdf

Centers for Disease Control and Prevention. (2014). Hepatitis C FAQs for health professionals. Retrieved from http://www.cdc.gov/hepatitis/HCV/HCVfaq.htm#section1

Centers for Disease Control and Prevention Division of Viral Hepatitis. (2015). Hepatitis in young persons who inject drugs (PWID). Retrieved from https://www.cdc.gov/hepatitis/outbreaks/youngpwid.htm

Chak, E., Talal, A. H., Sherman, K. E., Schiff, E. R., & Saab, S. (2011). Hepatitis C virus infection in USA: an estimate of true prevalence. *Liver International, 31*(8), 1090-1101. DOI: 10.1111/j.1478-3231.2011.02494.x

Chou, R., Hartung, D., Rahman, B., Wasson, N., Cottrell, E. B., & Fu, R. (2013). Comparative effectiveness of antiviral treatment for hepatitis C Virus infection in adults: A systematic review. *Annals of Internal Medicine, 158*(2), 114-123. DOI: 10.7326/0003-4819-158-2-201301150-00576

Denniston, M. M., Jiles, R. B., Drobeniuc, J., Klevens, R. M., Ward, J. W., McQuillan, G. M., & Holmberg, S. D. (2014). Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. *Annals of Internal Medicine, 160*(5), 293-300. DOI: 10.7326/m13-1133

Edlin, B. R., Eckhardt, B. J., Shu, M. A., Holmberg, S. D., & Swan, T. (2015). Toward a more accurate estimate of the prevalence of hepatitis C in the United States. *Hepatology, 62*(5), 1353-1363. DOI: 10.1002/hep.27978

El-Serag, H. B., Hampel, H., Yeh, C., & Rabeneck, L. (2002). Extrahepatic manifestations of hepatitis C among United States male veterans. *Hepatology, 36*(6), 1439-1445.

Feld, J. J., & Liang, T. J. (2006). Hepatitis C--identifying patients with progressive liver injury. *Hepatology, 43*(2 Suppl 1), S194-206. DOI: 10.1002/hep.21065

Gerrity, M., Carson, S., & Harrod, C. (2016). *Association of Metavir fibrosis scores and clinical outcomes*. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University.

Goodgame, B., Shaheen, N. J., Galanko, J., & El-Serag, H. B. (2003). The risk of end stage liver disease and hepatocellular carcinoma among persons infected with hepatitis C virus: Publication bias? *The American Journal of Gastroenterology, 98*(11), 2535-2542. DOI: 10.1111/j.1572-0241.2003.07678.x

Hellard, M., McBryde, E., Sacks Davis, R., Rolls, D. A., Higgs, P., Aitken, C., ... Robins, G. (2015). Hepatitis C transmission and treatment as prevention - The role of the injecting network. *The International Journal on Drug Policy, 26*(10), 958-962. DOI: 10.1016/j.drugpo.2015.05.006

Hezode, C., Roudot-Thoraval, F., Nguyen, S., Grenard, P., Julien, B., Zafrani, E. S., ... Mallat, A. (2005). Daily cannabis smoking as a risk factor for progression of fibrosis in chronic hepatitis C. *Hepatology, 42*(1), 63-71. DOI: 10.1002/hep.20733

Huang, Y., de Boer, W. B., Adams, L. A., MacQuillan, G., Bulsara, M. K., & Jeffrey, G. P. (2015). Clinical outcomes of chronic hepatitis C patients related to baseline liver fibrosis stage: A hospital-based linkage study. *Internal Medicine Journal, 45*(1), 48-54. DOI: 10.1111/imj.12626

Konerman, M. A., Yapali, S., & Lok, A. S. (2014). Systematic review: Identifying patients with chronic hepatitis C in need of early treatment and intensive monitoring--predictors and predictive models of disease progression. *Alimentary Pharmacology & Therapeutics, 40*(8), 863-879. DOI: http://dx.doi.org/10.1111/apt.12921

Koretz, R. L., Lin, K. W., Ioannidis, J. P., & Lenzer, J. (2015). Is widespread screening for hepatitis C justified? *BMJ, 350*, g7809. DOI: 10.1136/bmj.g7809

Levin, J. (2013). Prevalence, treatment, and comorbidities of hepatitis C infection (HCV) among patients with commercial and Medicaid insurance. *National AIDS Treatment Advocacy Project Digestive Disease Week,* . May 18-21, 2013, Retrieved from http://www.natap.org/2013/DDW/DDW_03.htm

Lok, A. S., Seeff, L. B., Morgan, T. R., di Bisceglie, A. M., Sterling, R. K., Curto, T. M., ... Goodman, Z. D. (2009). Incidence of hepatocellular carcinoma and associated risk factors in hepatitis C-related advanced liver disease. *Gastroenterology, 136*(1), 138-148. DOI: 10.1053/j.gastro.2008.09.014

Mallat, A., Hezode, C., & Lotersztajn, S. (2008). Environmental factors as disease accelerators during chronic hepatitis C. *Journal of Hepatology, 48*(4), 657-665. DOI: 10.1016/j.jhep.2008.01.004

Martin, N. K., Vickerman, P., Dore, G. J., & Hickman, M. (2015). The hepatitis C virus epidemics in key populations (including people who inject drugs, prisoners and MSM): The use of direct-acting antivirals as treatment for prevention. *Current Opinion in HIV and AIDS, 10*(5), 374-380. DOI: 10.1097/coh.0000000000000179

Milliman. (2015). The burden of hepatitic C virus disease in comercial and managed Medicaid populations. Retrieved from http://www.milliman.com/uploadedFiles/insight/2015/milliman-hcv-burden.pdf

Missiha, S. B., Ostrowski, M., & Heathcote, E. J. (2008). Disease progression in chronic hepatitis C: modifiable and nonmodifiable factors. *Gastroenterology, 134*(6), 1699-1714. DOI: 10.1053/j.gastro.2008.02.069

National Academies of Sciences, Engineering, & and Medicine. (2016). *Eliminating the public health problem of hepatitis B and C in the United States: Phase One report*. Washington (DC): National Academies Press (US).

Oregon Public Health Division. (2015). HCV: Just the facts, please *CD Summary* (Vol. 64). Portland, OR.

Padegimas, A., Forde, K. A., Goldberg, L. R., & Birati, E. Y. (2016). Myo-pericarditis secondary to ledipasvir-sofosbuvir therapy. *Journal of Hepatology, 64*(5), 1196-1198. DOI: http://dx.doi.org/10.1016/j.jhep.2016.01.015

Shiffman, M. L., & Benhamou, Y. (2015). Cure of HCV related liver disease. *Liver International, 35*, 71-77. DOI: 10.1111/liv.12734

Thein, H. H., Yi, Q., Dore, G. J., & Krahn, M. D. (2008). Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: A meta-analysis and meta-regression. *Hepatology, 48*(2), 418-431. DOI: http://dx.doi.org/10.1002/hep.22375

U.S. Food and Drug Adminstration. (2016). FDA Drug Safety Communication: FDA warns about the risk of hepatitis B reactivating in some patients treated with direct-acting antivirals for hepatitis C.

Vergniol, J., Boursier, J., Coutzac, C., Bertrais, S., Foucher, J., Angel, C., ... Cales, P. (2014). Evolution of noninvasive tests of liver fibrosis is associated with prognosis in patients with chronic hepatitis C. *Hepatology, 60*(1), 65-76. DOI: 10.1002/hep.27069

Williams, I. T., Bell, B. P., Kuhnert, W., & Alter, M. J. (2011). Incidence and transmission patterns of acute hepatitis C in the United States, 1982-2006. *Archives of Internal Medicine, 171*(3), 242-248. DOI: 10.1001/archinternmed.2010.511

Wu, H.-X., Wu, J., Wong, T., Donaldson, T., Dinner, K., Andonov, A., ... Paton, S. (2006). Enhanced surveillance of newly acquired hepatitis C virus infection in Canada, 1998 to 2004. *Scandinavian Journal of Infectious Diseases, 38*(6-7), 482-489. DOI: 10.1080/00365540500525161

Xu, F., Moorman, A. C., Tong, X., Gordon, S. C., Rupp, L. B., Lu, M., ... Holmberg, S. D. (2016). All-Cause Mortality and Progression Risks to Hepatic Decompensation and Hepatocellular Carcinoma in Patients Infected With Hepatitis C Virus. *Clinical Infectious Diseases 62*(3), 289-297. DOI: 10.1093/cid/civ860

Zeremski, M., Dimova, R. B., Pillardy, J., de Jong, Y. P., Jacobson, I. M., & Talal, A. H. (2016). Fibrosis progression in patients with chronic Hepatitis C virus infection. *The Journal of Infectious Diseases*. DOI: 10.1093/infdis/jiw332

Appendix A

Search Strategy 1:

Database: Ovid MEDLINE(R) without Revisions <1996 to December Week 1 2016>

Search Strategy:

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1 exp Hepatitis C/ or hepatitis c.mp. (60359)
2 hcv.mp. (37932)
3 1 and 2 (35231)
4 liver cirrhosis.mp. or exp Liver Cirrhosis/ (42939)
5 Fibrosis/ or fibrosis.mp. (105515)
6 liver.mp. or exp Liver/ (452628)
7 5 and 6 (22438)
8 4 or 7 (53372)
9 3 and 8 (5760)
10 limit 9 to (english language and humans and yr="2014 -Current") (996)
11 systematic reviews.mp. (12134)
12 meta-analysis.mp. or exp Meta-Analysis/ (94012)
13 11 and 12 (4185)
14 randomized controlled trial.mp. or Randomized Controlled Trial/ (335460)
15 cohort study.mp. or exp Cohort Studies/ (1251296)
16 13 or 14 or 15 (1496392)
17 10 and 16 (334)

Search Strategy 2:

Database: Ovid MEDLINE(R) without Revisions <1996 to August Week 1 2016>

1 hepatitis c.mp. or Hepatitis C, Chronic/ or Hepatitis C/ (59462)
2 metavir.mp. (844)
3 1 and 2 (612)
4 limit 3 to (english language and humans) (559)
5 limit 4 to yr="2015 -Current" (54)

Search Strategy 3:

Database: Ovid MEDLINE(R) without Revisions <1996 to December Week 1 2016>

Search Strategy:

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1 exp Hepatitis C/ or hepatitis c.mp. (60359)
2 hcv.mp. (37932)
3 1 and 2 (35231)

4 exp Aged/ or exp Cryoglobulinemia/ or Lymphoproliferative Disorders/ or extrahepatic manifestation.mp. (1722415)

5 3 and 4 (8054)

6 limit 5 to (english language and humans) (7487)

7 limit 6 to clinical study (6)

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The Center for Evidence-based Policy (Center) is recognized as a national leader in evidence-based decision making and policy design. The Center understands the needs of policymakers and supports public organizations by providing reliable information to guide decisions, maximize existing resources, improve health outcomes, and reduce unnecessary costs. The Center specializes in ensuring that diverse and relevant perspectives are considered and appropriate resources are leveraged to strategically address complex policy issues with high-quality evidence and collaboration. The Center is based at Oregon Health & Science University in Portland, Oregon.

The Medicaid Evidence-based Decisions Project (MED) is housed at the Center. Its mission is to create an effective collaboration among Medicaid programs and their state partners for the purpose of making high-quality evidence analysis available to support benefit design and coverage decisions made by state programs. Further information about MED project and the Center is available at www.ohsu.edu/policycenter.

Suggested citation: Gerrity, M., Harrod, C., King, V. (2016). *Treating hepatitis C at liver fibrosis stage F2 versus F3*. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University.

Conflict of Interest Disclosures: No authors have conflicts of interest to disclose. All authors have completed and submitted the Oregon Health & Science University form for Disclosure of Potential Conflicts of Interest, and none were reported.

Funding/Support: This research was funded by the Center for Evidence-based Policy's Medicaid Evidence-based Decisions project at Oregon Health & Science University.

This document was prepared by the Center for Evidence-based Policy at Oregon Health & Science University (Center). This document is intended to support Medicaid Evidence-based Decisions (MED) project participant organizations and their constituent decision-making bodies to make informed decisions about the provision of health care services. The document is intended as a reference and is provided with the understanding that 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, the MED project, or MED participating organizations. Researchers and authors involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

Annals of Internal Medicine ORIGINAL RESEARCH

Cost-Effectiveness of Novel Regimens for the Treatment of Hepatitis C Virus

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Background: New regimens for hepatitis C virus (HCV) have shorter treatment durations and increased rates of sustained virologic response compared with existing therapies but are extremely expensive.

Objective: To evaluate the cost-effectiveness of these treatments under different assumptions about their price and efficacy.

Design: Discrete-event simulation.

Data Sources: Published literature.

Target Population: Treatment-naive patients infected with chronic HCV genotype 1, 2, or 3.

Time Horizon: Lifetime.

Perspective: Societal.

Intervention: Usual care (boceprevir–ribavirin–pegylated interferon [PEG]) was compared with sofosbuvir–ribavirin–PEG and 3 PEG-free regimens: sofosbuvir–simeprevir, sofosbuvir–daclatasvir, and sofosbuvir–ledipasvir. For genotypes 2 and 3, usual care (ribavirin–PEG) was compared with sofosbuvir–ribavirin, sofosbuvir–daclatasvir, and sofosbuvir–ledipasvir–ribavirin (genotype 3 only).

Outcome Measures: Discounted costs (in 2014 U.S. dollars), quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios.

Results of Base-Case Analysis: Assuming sofosbuvir, simeprevir, daclatasvir, and ledipasvir cost $7000, $5500, $5500, and $875 per week, respectively, sofosbuvir–ledipasvir was cost-effective for genotype 1 and cost $12 825 more per QALY than usual care. For genotype 2, sofosbuvir–ribavirin and sofosbuvir–daclatasvir cost $110 000 and $691 000 per QALY, respectively. For genotype 3, sofosbuvir–ledipasvir–ribavirin cost $73 000 per QALY, sofosbuvir–ribavirin was more costly and less effective than usual care, and sofosbuvir–daclatasvir cost more than $396 000 per QALY at assumed prices.

Results of Sensitivity Analysis: Sofosbuvir–ledipasvir was the optimal strategy in most simulations for genotype 1 and would be cost-saving if sofosbuvir cost less than $5500. For genotype 2, sofosbuvir–ribavirin–PEG would be cost-saving if sofosbuvir cost less than $2250 per week. For genotype 3, sofosbuvir–ledipasvir–ribavirin would be cost-saving if sofosbuvir cost less than $1500 per week.

Limitation: Data are lacking on real-world effectiveness of new treatments and some prices.

Conclusion: From a societal perspective, novel treatments for HCV are cost-effective compared with usual care for genotype 1 and probably genotype 3 but not for genotype 2.

Primary Funding Source: CVS Health.

Ann Intern Med. 2015;162:407-419. doi:10.7326/M14-1152 **www.annals.org**
For author affiliations, see end of text.

Drug therapies for hepatitis C virus (HCV) infection have been available for more than a decade. Despite approval of the protease inhibitors boceprevir and telaprevir in 2011, which have substantially increased rates of sustained virologic response (SVR) for patients infected with HCV genotype 1, many patients do not complete recommended treatment owing to shortcomings of pegylated interferon (PEG) (1).

Several new regimens may represent important improvements over current HCV treatments. The once-daily nucleotide polymerase inhibitor sofosbuvir (Sovaldi, Gilead Sciences) was approved in December 2013 (2) to be used in combination with ribavirin and PEG in treatment-naive patients infected with HCV genotypes 1 and 4 and with ribavirin alone in patients infected with HCV genotypes 2 and 3. Sofosbuvir can achieve higher SVR rates in substantially shorter treatment times than existing regimens (3–6). Shorter treatment durations and higher SVR rates, even among nonresponders, also seem possible with other PEG-free regimens consisting of sofosbuvir in combination with simeprevir (7, 8), daclatasvir (9), or ledipasvir (10–13).

Despite their promise, these novel therapies are very expensive and, considering that more than 3 million patients (14) may be eligible for these therapies, the budgetary implications have generated widespread concern (15, 16). Little is known about the relative societal health benefit and value of the new treatments for hepatitis C compared with current options. Therefore, we conducted a cost-effectiveness analysis to evaluate the balance between health benefit and health care expenditures for these treatments under different assumptions about their price and efficacy.

Methods

We developed a discrete-event simulation (DES) model using Arena, version 12.00 (Rockwell Automation), to simulate the natural history and progression of liver disease among treatment-naive patients infected

See also:

Related article 397

Web-Only

Supplement

Appl Health Econ Health Policy
DOI 10.1007/s40258-016-0261-2

ORIGINAL RESEARCH ARTICLE

Assessing the Effect of Potential Reductions in Non-Hepatic Mortality on the Estimated Cost-Effectiveness of Hepatitis C Treatment in Early Stages of Liver Disease

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Abstract

Background Most cost-effectiveness analyses of hepatitis C (HCV) therapy focus on the benefits of reducing liver-related morbidity and mortality.

Objectives Our objective was to assess how cost-effectiveness estimates of HCV therapy can vary depending on assumptions regarding the potential impact of HCV therapy on non-hepatic mortality.

Methods We adapted a state-transition model to include potential effects of HCV therapy on non-hepatic mortality. We assumed successful treatment could reduce non-hepatic mortality by as little as 0 % to as much as 100 %. Incremental cost-effectiveness ratios were computed comparing immediate treatment versus delayed treatment and comparing immediate treatment versus non-treatment.

Results Comparing immediate treatment versus delayed treatment, when we included a 44 % reduction in non-hepatic mortality following successful HCV treatment, the incremental cost per quality-adjusted life year (QALY) gained by HCV treatment fell by 76 % (from US$314,100 to US$76,900) for patients with no fibrosis and by 43 % (from US$62,500 to US$35,800) for patients with moderate fibrosis. Comparing immediate treatment versus non-treatment, assuming a 44 % reduction in non-hepatic mortality following successful HCV treatment, the incremental cost per QALY gained by HCV treatment fell by 64 % (from US$186,700 to US$67,300) for patients with no fibrosis and by 27 % (from US$35,000 to US$25,500) for patients with moderate fibrosis.

Conclusion Including reductions in non-hepatic mortality from HCV treatment can have substantial effects on the estimated cost-effectiveness of treatment.

Key Points for Decision Makers

HCV treatment models vary in the way they incorporate non-hepatic mortality.

Assumptions regarding reductions in non-hepatic mortality from HCV treatment can have substantial effects on estimated cost-effectiveness ratios.

1 Introduction

Hepatitis C virus (HCV) infection is associated with increased patient morbidity and mortality [1–5]. In a large sample of people with HCV infection in the USA with a median age of 52 years, the annual probability of all-cause mortality was estimated to be 0.014 among individuals with minimal liver disease and 0.073 among individuals with severe liver disease [6]. By contrast, among the US

Disclaimer The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Electronic supplementary material The online version of this article (doi:10.1007/s40258-016-0261-2) contains supplementary material, which is available to authorized users.

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Published online: 01 August 2016

Scoring Criteria Guidelines for the HERC Individual and Population Health Impact Measures

Impact on Healthy Life

0 – No impact on health
1 – Nonfatal with a marginal impact on health
2 – Nonfatal with a modest impact on health
3 – Nonfatal with a low probability of a significant residual effect or a high probability of a residual effect with a moderate impact on health
4 – Nonfatal with low probability (<20%) of significant disability (e.g., blindness) or at least a moderate probability of a significant residual effect
5 – Nonfatal, but at least moderate (>20%) probability of significant disability; Very low fatality (<1%)
6 – Low fatality (1-5%)
7 – Moderate fatality (5-20%)
8 – Significant fatality (20-50%)
9 – High fatality (50-90%)
10 – Very high fatality (>90%)

Impact on Pain and Suffering

0 – No impact on pain or suffering
1 – Intermittent pain of moderate level or frequent pain of low level and/or low level of suffering of the individual, immediate family or caregiver
2 – Frequent pain of moderate level or constant pain of low level and/or modest level of suffering of the individual, immediate family or caregiver
3 – Intermittent pain of high level or constant pain of moderate level and/or moderate level of suffering of the individual, immediate family or caregiver
4 – Frequent pain of high level and/or high level of suffering of the individual, immediate family or caregiver
5 – Constant pain of high level and/or extreme suffering of the individual, immediate family or caregiver

Population Effects

0 – No impact on population health
1 – Nontreatment would result in limited spread of a significant nonfatal disease or have a low impact on population safety (e.g. due to the nontreatment of a mental health condition)
2 – Nontreatment would result in a moderate spread of a significant nonfatal disease or have a modest impact on population safety
3 – Nontreatment would result in a limited spread of a potentially fatal disease or a wide spread of a significant nonfatal disease or have a moderate impact on population safety
4 – Nontreatment would result in a moderate spread of a potentially fatal disease or have a high impact on population safety
5 – Nontreatment would result in a wide spread of a potentially fatal disease or have a very high impact on population safety

Scoring Criteria Guidelines for the HERC Individual and Population Health Impact Measures

Impact on Vulnerable Populations

0 – No impact on vulnerable populations
1 – Somewhat disproportionate impact of a condition with a moderate impact on health on one or more vulnerable populations (does not include men, women, children, pregnant women considered as separate populations, nor low-income individuals, since methodology is only being applied to Medicaid population at this point)
2 – Moderately disproportionate impact of a condition with a moderate impact on health on one or more vulnerable populations
3– Somewhat disproportionate impact of a condition with a significant impact on health on one or more vulnerable populations
4 – Moderately disproportionate impact of a condition with a significant impact on health on one or more vulnerable populations
5 – Highly disproportionate impact of a condition with a significant impact on health on one or more vulnerable populations

Tertiary Prevention

0 – No tertiary prevention provided by treatment and early treatment does not prevent progression of the disease
1 – Treatment will prevent of moderate complication and/or early treatment may prevent progression of the disease resulting in a moderate impact on health
2 – Low to modest likelihood that treatment will prevent a significant complication or prevent progression of the disease resulting in significant impact on health
3 –Moderate to high likelihood that treatment will prevent a significant complication or prevent progression of the disease resulting in significant impact on health
4 – Low to modest likelihood that treatment will prevent severely debilitating complication and/or early treatment with prevent progression of disease leading to severe disability or death
5 – Moderately to high likelihood that treatment will prevent severely debilitating complication and/or early treatment with prevent progression of disease leading to severe disability or death

Effectiveness

0 – No demonstrated effectiveness (<5%) or causes harm
1 - Achieves desired result in 5-25% of cases
2 - Achieves desired result in 25-50% of cases
3 – Achieves desired result in 50-75% of cases
4 – Achieves desired result in 75-95% of cases
5 – Achieves desired result in 95+% of cases

Net Cost

0 – Very high cost (>$100,000)
1 – High cost ($20,000-$100,000)
2 – Moderate cost ($5,000-$20,000) or higher cost somewhat offset by cost of treatment alternative
3 – Modest cost ($1,000-$5,000) or higher cost significantly offset by cost of treatment alternative
4 – Low cost (<$1,000) or higher cost nearly offset by cost of treatment alternative
5 – Cost savings

Injuries to Blood Vessels of the Extremities, Neck, Thorax and Abdomen

Question: Where should injuries to blood vessels of the extremities, neck, thorax and abdomen be prioritized?

Question source: HERC staff

Issue: Placement of injury of blood vessels of the neck was reviewed in May, 2014 as part of the 2015 Biennial review. At that time, VBBS/HERC moved the diagnoses of neck injuries form line 135 CRUSH INJURIES OTHER THAN DIGITS; COMPARTMENT SYNDROME to line 82 INJURY TO MAJOR BLOOD VESSELS OF EXTREMITIES, and changed the line title of line 82 to 82 INJURY TO MAJOR BLOOD VESSELS OF EXTREMITIES AND NECK. However, only some of the ICD-10 codes for injuries to major blood vessels were identified and moved.

With the Biennial Review January 1, 2015 Prioritized List, the line title of line 135 changed from 135 CRUSH INJURIES OTHER THAN DIGITS; COMPARTMENT SYNDROME to 135 CRUSH INJURIES OTHER THAN DIGITS; COMPARTMENT SYNDROME; INJURIES TO BLOOD VESSEL(S) OF THE NECK. No mention of the addition of INJURIES TO BLOOD VESSEL(S) OF THE NECK to this line was found in the minutes. It is possible that the general surgery ICD-10 review group suggested this change; no documentation of that meeting was found.

It is clear from minutes that the intent of the HSC/HERC is to prioritize injuries of the major blood vessels of the extremities and of the neck on a high line. There is also mention in the minutes of prioritizing minor blood vessel injuries (i.e., of the feet) to a low line (not line 135).

Injuries of blood vessels of the thoracic cavity is on a lower line, 280 INJURY TO BLOOD VESSELS OF THE THORACIC CAVITY. This was reviewed in 2014, and felt to be appropriate due to the lower effectiveness of treatment for these types of injuries.

It was also noted during the review of line 135 that it contained the only entry for ICD-10 codes for many of the injuries to major blood vessels of the chest/thorax/abdomen (i.e. aorta, renal artery, axillary artery, etc.). Most of the CPT repair codes for these types of internal major vessel injuries appear on line 84 INJURY TO INTERNAL ORGANS or 281 INJURY TO BLOOD VESSELS OF THE THORACIC CAVITY. Line 281 contains a much more extensive list of CPT codes for repair of blood vessels in the chest and abdomen compared to line 84. Line 135 only contains a few CPT codes for such repairs.

HERC staff recommendations:

1) Per the previous intent of the HERC, remove head/neck and major extremity blood vessel injury ICD-10 codes from line 135 CRUSH INJURIES OTHER THAN DIGITS; COMPARTMENT SYNDROME; INJURIES TO BLOOD VESSEL(S) OF THE NECK and consolidate into line 82 INJURY TO MAJOR BLOOD VESSELS OF EXTREMITIES AND NECK
    a. See the table below
    b. Injuries to finger/toe blood vessels moved to more appropriate lines if not already present on such lines per past intent of the HSC/HERC
    c. Change the title of line 135
        i. 135 CRUSH INJURIES OTHER THAN DIGITS; COMPARTMENT SYNDROME~~; INJURIES TO BLOOD VESSEL(S) OF THE NECK~~
    d. Remove blood vessel repair CPT codes from line 135 as shown in the tables below
2) Remove the thoracic/abdominal major blood vessel injury ICD-10 codes from line 135 CRUSH INJURIES OTHER THAN DIGITS; COMPARTMENT SYNDROME; INJURIES TO BLOOD VESSEL(S) OF THE NECK and place on line 281 INJURY TO BLOOD VESSELS OF THE THORACIC CAVITY
    a. See table below
    b. Allows pairing with appropriate repair CPT codes
    c. Change the title of line 281
        i. 281 INJURY TO BLOOD VESSELS OF THE THORACIC AND ABDOMINAL CAVIT~~Y~~IES
3) Consider reprioritizing line 281 as shown below
    a. As the scoring for line 281 results in a reprioritization at approximately line 107, consider merging lines 82 and 107 into "INJURIES TO MAJOR BLOOD VESSEL(S)"
        i. Include all current CPT codes on both lines
        ii. Prioritize at line 82

Line scoring:

Line 281 INJURY TO BLOOD VESSELS OF THE THORACIC AND ABDOMINAL CAVIT~~Y~~IES (current scores in parentheses)
Category 6 (6)
Impact on healthy life: 8 (8)
Pain/Suffering: 2 (2) [line 84 score=3; line 82=2]
Population effects: 0 (0)
Vulnerable population: 0 (0)
Tertiary Prevention: 4 (0) [line 84 score=4]
Effectiveness: 4 (3) [line 84 score=4; line 82=5]
Need for services: 1 (1)
Cost: 3 (3)
Score: 2240 (1200)
Line 107 (281)

Line 82 INJURY TO MAJOR BLOOD VESSELS OF EXTREMITIES AND NECK
Line 84 INJURY TO INTERNAL ORGANS

Injuries to Blood Vessels of the Extremities, Neck, Thorax and Abdomen

ICD-10 Codes for blood vessel injury appearing on lines 82 and/or 135

ICD-10 Code	Code description	Recommended Placement
S09.0XX	Injury of blood vessels of head, not elsewhere classified	82 ~~135~~
S45.0	Injury of axillary artery	82 ~~135~~
S45.1	Injury of brachial artery	82 ~~135~~
S45.2	Injury of axillary or brachial vein	82 ~~135~~
S45.3	injury of superficial vein at shoulder and upper arm level	82 ~~135~~
S45.8	injury of other specified blood vessels at shoulder and upper arm level	82 ~~135~~
S45.9	injury of unspecified blood vessel at shoulder and upper arm level	82 ~~135~~
S55.0	injury of ulnar artery	82 ~~135~~
S55.1	injury of radial artery	82 ~~135~~
S55.2	injury of vein at forearm level	82 ~~135~~
S55.8	injury of other blood vessels at forearm level	82 ~~135~~
S55.9	injury of unspecified blood vessel at forearm level	82 ~~135~~
S65.0	injury of ulnar artery at wrist and hand level	82 ~~135~~
S65.1	injury of radial artery at wrist and hand level	82 ~~135~~
S65.2	injury of superficial palmar arch	82 ~~135~~
S65.3	injury of deep palmar arch	82 ~~135~~
S65.4	injury of blood vessel of thumb	~~82~~ 294
S65.5	injury of blood vessel of finger	~~82~~ 294
S65.8	injury of other blood vessels at wrist and hand level	82 ~~135~~
S65.9	injury of unspecified blood vessel at wrist and hand level	82 ~~135~~
S75.0	injury of femoral artery	82 ~~135~~
S75.1	injury of femoral vein at hip and thigh level	82 ~~135~~
S75.2	injury of greater saphenous vein at hip and thigh level	82 ~~135~~
S75.8	injury of other blood vessels at hip and thigh level	82 ~~135~~
S75.9	injury of unspecified blood vessel at hip and thigh level	82 ~~135~~
S85.0	injury of popliteal artery	82 ~~135~~
S85.1	injury of tibial artery	82 ~~135~~
S85.2	injury of peroneal artery	82 ~~135~~
S85.3	injury of greater saphenous vein at lower leg level	82 ~~135~~
S85.4	injury of lesser saphenous vein at lower leg level	82 ~~135~~
S85.5	injury of popliteal vein	82 ~~135~~
S85.8	injury of other blood vessels at lower leg level	82 ~~135~~
S85.9	injury of unspecified blood vessel at lower leg level	82 ~~135~~
S95.0	injury of dorsal artery	~~135~~ 212
S95.1	injury of plantar artery	~~135~~ 212
S95.2	injury of dorsal vein	~~135~~ 212
S95.8	injury of other blood vessels at ankle and foot level	~~135~~ 212
S95.9	injury of unspecified blood vessel at ankle and foot level	~~135~~ 212

212 DEEP OPEN WOUND, WITH OR WITHOUT TENDON OR NERVE INVOLVEMENT

294 CRUSH AND OTHER INJURIES OF DIGITS

Injuries to Blood Vessels of the Extremities, Neck, Thorax and Abdomen

Relevant CPT codes appearing on line 82 and/or line 135

CPT	Code Description	Comments
35206	Repair blood vessel, direct; upper extremity	82,~~135~~,285
35207	Repair blood vessel, direct; hand, finger	82,~~135~~,285,294
35236	Repair blood vessel with vein graft; upper extremity	82,~~135~~,285
35266	Repair blood vessel with graft other than vein; upper extremity	82,~~135~~,285
35521	Bypass graft, with vein; axillary-femoral	~~135~~,240,290,354
37618	Ligation, major artery (eg, post-traumatic, rupture); extremity	82,~~135~~,330

285 BUDD-CHIARI SYNDROME, AND OTHER VENOUS EMBOLISM AND THROMBOSIS
330 NON-DISSECTING ANEURYSM WITHOUT RUPTURE

Major internal blood vessel ICD-10 codes on line 135

ICD-10 code	Code description	Recommended Placement
S27.9XX	Injury of unspecified intrathoracic organ	~~135~~ 281
S35.0	injury of abdominal aorta	~~135~~ 281
S35.1	injury of inferior vena cava	~~135~~ 281
S35.2	injury of celiac/inferior mesenteric/superior mesenteric artery	~~135~~ 281
S35.3	injury of portal/splenic/superior mesenteric/inferior mesenteric vein	~~135~~ 281
S35.4	injury of renal artery/vein	~~135~~ 281
S35.5	Injury of iliac artery/vein, uterine artery/vein, other vessels of lower abdomen or pelvis	~~135~~ 281

2018 Biennial Review
Secondary and Ill-Defined Malignancies

Question: Should the secondary and ill-defined malignancies line be reprioritized, or should some diagnoses on this line be moved to other, covered lines?

Question source: OHP medical directors, HERC staff

Issue: Line 595 SECONDARY AND ILL-DEFINED MALIGNANT NEOPLASMS contains approximately 50 cancer diagnoses; none of which are currently eligible for any treatment due to the low priority position of this line. Most of these diagnoses have a very poor prognosis even with treatment. Other diagnoses are very vague or unspecified.

Historically, these cancers were put below the funding line based on poor prognosis; they were expected to have less than a 5% 5-year survival, and then kept there because they were not expected to respond to treatments to meet the extended life expectancy requirements of the original language in GN12 TREATMENT OF CANCER WITH LITTLE OR NO BENEFIT. GN12 was revised a few years ago to specify that palliative care is always covered for cancers, but that treatment with intent to prolong survival is not covered only for patients with severe co-morbidities or very poor performance status (i.e. unlikely to survive treatment).

HERC staff have received multiple questions about why certain cancers appear on line 595. All other cancers, even those with poor prognosis such as pancreatic cancer, are in the funded area of the Prioritized List. Many secondary cancer or ill-defined cancer diagnosis codes are actually currently on other cancer lines. It is the custom with the List that very vague diagnoses, such as unspecified diagnoses, be placed on low priority lines to encourage more specific coding.

STATEMENT OF INTENT 1: PALLIATIVE CARE and GN12 TREATMENT OF CANCER WITH LITTLE OR NO BENEFIT are shown below. The diagnoses included in line 595 are also shown below in the table.

2018 Biennial Review
Secondary and Ill-Defined Malignancies

HERC staff recommendations:

1) **Option 1**: move the majority of diagnoses on line 595 SECONDARY AND ILL-DEFINED MALIGNANT NEOPLASMS onto other, covered cancer lines with similar organ type. Leave only completely unspecified diagnoses on line 595.
    a. See the table below for recommended code movements
        i. ICD-10 C26.1 (Malignant neoplasm of spleen) needs discussion as extremely poor prognosis even with treatment
        ii. Blank box indicates recommendation is to leave on line 595
    b. Rename line 595 ~~SECONDARY AND~~ ILL-DEFINED MALIGNANT NEOPLASMS
        i. Most secondary neoplasms will move to other lines
    c. Do not reprioritize as the extremely vague diagnoses remaining on this line are appropriately low priority
2) **Option 2**: reprioritize line 595.
    a. Suggested line scoring shown below
    b. Palliative care would still be covered as in SOI1
3) **Option 3**: make no changes

Line scoring:
Line 595 SECONDARY AND ILL-DEFINED MALIGNANT NEOPLASMS (current scores in parentheses)
Category 9 (9)
Impact on healthy life: 8 (7)
Pain/Suffering: 5 (5)
Population effects: 0 (0)
Vulnerable population: 0 (0)
Tertiary Prevention:
Effectiveness: 1 (1)
Need for services: 1 (1)
Cost: 1 (1)
Score: 40 (12)
Line 566 (595)

2018 Biennial Review
Secondary and Ill-Defined Malignancies

ICD-10 Code	Code Description	Suggested Alternate Placement	Comments
C26.0	Malignant neoplasm of intestinal tract, part unspecified	161 CANCER OF COLON, RECTUM, SMALL INTESTINE AND ANUS	
C26.1	Malignant neoplasm of spleen	198 HEREDITARY ANEMIAS, HEMOGLOBINOPATHIES, AND DISORDERS OF THE SPLEEN Alternative: leave on line 595	Very rare, extremely poor prognosis. Only treatment is splenectomy, not responsive to chemotherapy. Prognoses extremely poor (3-6 months) even with surgery. Line 198 contains radical splenectomy CPT codes
C26.9	Malignant neoplasm of ill-defined sites within the digestive system		Too vague. Would need to be on stomach cancer and intestinal cancer lines.
C45.7	Mesothelioma of other sites		Mesothelioma of pleura, pericardium, and peritoneum on three separate covered lines
C45.9	Mesothelioma, unspecified		Too vague
C7A.1	Malignant poorly differentiated neuroendocrine tumors	264 CANCER OF ENDOCRINE SYSTEM, EXCLUDING THYROID; CARCINOID SYNDROME	C7A.00 (Malignant carcinoid tumor of unspecified site) is on line 264. Other malignant carcinoid tumors are on various GI cancer lines
C7A.8	Other malignant neuroendocrine tumors	264	See above
C7B.00	Secondary carcinoid tumors, unspecified site	264	
C7B.01	Secondary carcinoid tumors of distant lymph nodes	264	
C7B.02	Secondary carcinoid tumors of liver	320 CANCER OF LIVER	C78.7 (Secondary malignant neoplasm of liver and intrahepatic bile duct) is on line 320
C7B.03	Secondary carcinoid tumors of bone	205 CANCER OF BONES	C79.51 (Secondary malignant neoplasm of bone) is on line 205

C7B.04	Secondary carcinoid tumors of peritoneum	266 CANCER OF RETROPERITONEUM, PERITONEUM, OMENTUM AND MESENTERY	
C7B.09	Secondary carcinoid tumors of other sites	264	
C7B.1	Secondary Merkel cell carcinoma	280 CANCER OF SKIN, EXCLUDING MALIGNANT MELANOMA	All other Merkel cell carcinoma ICD-10 codes on line 280
C7B.8	Other secondary neuroendocrine tumors	264	
C76.1	Malignant neoplasm of thorax		Too vague
C76.2	Malignant neoplasm of abdomen		Too vague
C76.3	Malignant neoplasm of pelvis		Too vague
C76.40	Malignant neoplasm of unspecified upper limb		Too vague
C76.41	Malignant neoplasm of right upper limb		Too vague
C76.42	Malignant neoplasm of left upper limb		Too vague
C76.50	Malignant neoplasm of unspecified lower limb		Too vague
C76.51	Malignant neoplasm of right lower limb		Too vague
C76.52	Malignant neoplasm of left lower limb		Too vague
C76.8	Malignant neoplasm of other specified ill-defined sites		Too vague
C77.0	Secondary and unspecified malignant neoplasm of lymph nodes of head, face and neck		Too vague – could relate to any type of cancer that has metastasized Alternative: C96.Z (Other specified malignant neoplasms of lymphoid, hematopoietic and related tissue) is on lines 162,167 Non-Hodgkins Lymphoma
C77.1	Secondary and unspecified malignant neoplasm of intrathoracic lymph nodes		Too vague

C77.2	Secondary and unspecified malignant neoplasm of intra-abdominal lymph nodes		Too vague
C77.3	Secondary and unspecified malignant neoplasm of axilla and upper limb lymph nodes		Too vague
C77.4	Secondary and unspecified malignant neoplasm of inguinal and lower limb lymph nodes		Too vague
C77.5	Secondary and unspecified malignant neoplasm of intrapelvic lymph nodes		Too vague
C77.8	Secondary and unspecified malignant neoplasm of lymph nodes of multiple regions		Too vague
C77.9	Secondary and unspecified malignant neoplasm of lymph node, unspecified		Too vague
C78.00	Secondary malignant neoplasm of unspecified lung	267 CANCER OF LUNG, BRONCHUS, PLEURA, TRACHEA, MEDIASTINUM AND OTHER RESPIRATORY ORGANS	
C78.01	Secondary malignant neoplasm of right lung	267	
C78.02	Secondary malignant neoplasm of left lung	267	
C78.1	Secondary malignant neoplasm of mediastinum	267	
C78.2	Secondary malignant neoplasm of pleura	267	
C78.30	Secondary malignant neoplasm of unspecified respiratory organ	267	
C78.39	Secondary malignant neoplasm of other respiratory organs	267	
C78.4	Secondary malignant neoplasm of small intestine	161 CANCER OF COLON, RECTUM, SMALL INTESTINE AND ANUS	

2018 Biennial Review
Secondary and Ill-Defined Malignancies

C78.5	Secondary malignant neoplasm of large intestine and rectum	161	
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum	266 CANCER OF RETROPERITONEUM, PERITONEUM, OMENTUM AND MESENTERY	
C78.80	Secondary malignant neoplasm of unspecified digestive organ		Too vague
C78.89	Secondary malignant neoplasm of other digestive organs		Too vague
C79.81	Secondary malignant neoplasm of breast	195 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER	
C79.82	Secondary malignant neoplasm of genital organs	291 CANCER OF VAGINA, VULVA, AND OTHER FEMALE GENITAL ORGANS 263 CANCER OF PENIS AND OTHER MALE GENITAL ORGANS	
C79.89	Secondary malignant neoplasm of other specified sites		Too vague. Used for many, many types of cancers
C79.9	Secondary malignant neoplasm of unspecified site		Too vague
C80.0	Disseminated malignant neoplasm, unspecified		Too vague
C80.1	Malignant (primary) neoplasm, unspecified		Too vague
D44.9	Neoplasm of uncertain behavior of unspecified endocrine gland		Too vague
Z85.020	Personal history of malignant carcinoid tumor of stomach	220 CANCER OF STOMACH	

2018 Biennial Review
Secondary and Ill-Defined Malignancies

Z85.030	Personal history of malignant carcinoid tumor of large intestine	161 CANCER OF COLON, RECTUM, SMALL INTESTINE AND ANUS	
Z85.040	Personal history of malignant carcinoid tumor of rectum	161	
Z85.060	Personal history of malignant carcinoid tumor of small intestine	161	
Z85.110	Personal history of malignant carcinoid tumor of bronchus and lung	267 CANCER OF LUNG, BRONCHUS, PLEURA, TRACHEA, MEDIASTINUM AND OTHER RESPIRATORY ORGANS	
Z85.230	Personal history of malignant carcinoid tumor of thymus	Informational Diagnosis File	Other history of thymus cancers is Informational
Z85.520	Personal history of malignant carcinoid tumor of kidney	219 CANCER OF KIDNEY AND OTHER URINARY ORGANS	
Z85.821	Personal history of Merkel cell carcinoma	292 CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX	
Z85.858	Personal history of malignant neoplasm of other endocrine glands	Informational Diagnosis File	Too vague

STATEMENT OF INTENT 1: PALLIATIVE CARE

It is the intent of the Commission that palliative care services be covered for patients with a life-threatening illness or severe advanced illness expected to progress toward dying, regardless of the goals for medical treatment and with services available according to the patient's expected length of life (see examples below).

Palliative care is comprehensive, specialized care ideally provided by an interdisciplinary team (which may include but is not limited to physicians, nurses, social workers, etc.) where care is particularly focused on alleviating suffering and promoting quality of life. Such interdisciplinary care should include assessment, care planning, and care coordination, emotional and psychosocial counseling for patients and families, assistance accessing services from other needed community resources, and should reflect the patient and family's values and goals.

Some examples of palliative care services that should be available to patients with a life-threatening/limiting illness,

A) without regard to a patient's expected length of life:
   - Inpatient palliative care consultation; and,
   - Outpatient palliative care consultation, office visits.

B) with an expected median survival of less than one year, as supported by the best available published evidence:
   - Home-based palliative care services (to be defined by DMAP), with the expectation that the patient will move to home hospice care.

C) with an expected median survival of six months or less, as supported by peer-reviewed literature:
   - Home hospice care, where the primary goal of care is quality of life (hospice services to be defined by DMAP).

It is the intent of the Commission that certain palliative care treatments be covered when these treatments carry the primary goal to alleviate symptoms and improve quality of life, without intending to alter the trajectory of the underlying disease.

Some examples of covered palliative care treatments include:

A) Radiation therapy for painful bone metastases with the intent to relieve pain and improve quality of life.
B) Surgical decompression for malignant bowel obstruction.
C) Medication therapy such as chemotherapy with low toxicity/low side effect agents with the goal to decrease pain from bulky disease or other identified complications. Cost of chemotherapy and alternative medication(s) should also be considered.
D) Medical equipment and supplies (such as non-motorized wheelchairs, walkers, bandages, and catheters) determined to be medically appropriate for completion of basic activities of daily living, for management of symptomatic complications or as required for symptom control.
E) Acupuncture with intent to relieve nausea.

Cancer treatment with intent to palliate is not a covered service when the same palliation can be achieved with pain medications or other non-chemotherapy agents.

It is NOT the intent of the Commission that coverage for palliative care encompasses those treatments that seek to prolong life despite substantial burdens of treatment and limited chance of benefit. See Guideline Note 12 TREATMENT OF CANCER WITH LITTLE OR NO BENEFIT.

GUIDELINE NOTE 12, TREATMENT OF CANCER WITH LITTLE OR NO BENEFIT

Lines 97,116-120,129,133,137,139,161,162,167,183,195,204,205,213,215,219,220,222,234,239,242, 243,263-267,275,280,291,292,299,319-321,334,377,402,403,424,439,595,606

Cancer is a complex group of diseases with treatments that vary depending on the specific subtype of cancer and the patient's unique medical and social situation. Goals of appropriate cancer therapy can vary from intent to cure, disease burden reduction, disease stabilization and control of symptoms. Cancer care must always take place in the context of the patient's support systems, overall heath, and core values. Patients should have access to appropriate peer-reviewed clinical trials of cancer therapies. A comprehensive multidisciplinary approach to treatment should be offered including palliative care services (see Statement of Intent 1, Palliative Care).

Treatment with intent to prolong survival is not a covered service for patients who have progressive metastatic cancer with

A) severe co-morbidities unrelated to the cancer that result in significant impairment in two or more major organ systems which would affect efficacy and/or toxicity of therapy; OR
B) a continued decline in spite of best available therapy with a non reversible Karnofsky Performance Status or Palliative Performance score of <50% with ECOG performance status of 3 or higher which are not due to a pre-existing disability.

Treatment with intent to relieve symptoms or improve quality of life is a covered service as outlined in Statement of Intent 1, Palliative Care.

To qualify for treatment coverage, the cancer patient must have a documented discussion about treatment goals, treatment prognosis and the side effects, and knowledge of the realistic expectations of treatment efficacy. This discussion may take place with the patient's oncologist, primary care provider, or other health care provider, but preferably in a collaborative interdisciplinary care coordination discussion. Treatment must be provided via evidence-driven pathways (such as NCCN, ASCO, ASH, ASBMT, or NIH Guidelines) when available.

Section 6.0

Coverage Guidances

DIGITAL BREAST TOMOSYNTHESIS FOR BREAST CANCER SCREENING IN AVERAGE RISK WOMEN

Coverage Guidance for VbBS Consideration

February 2, 2017

Oregon Health Authority

OREGON HEALTH & SCIENCE UNIVERSITY

Center For Evidence-based Policy

Background

- 1 in 8 women (12%) develop invasive breast cancer during their lifetime
- Breast cancer death rate has steadily declined in last 15 years; decline in breast cancer mortality attributed to
  - Screening efforts leading to earlier cancer detection
  - Fewer women using hormone therapy after menopause
  - Improved quality of treatment

Background

- Systematic review and meta-analysis of randomized controlled trials of screening for breast cancer, conducted by Nelson et al. (2016) for USPSTF:
  - Screening mammography reduces breast cancer mortality, but not all-cause mortality
- USPSTF recommendations for mammography:
  - Grade “B” recommendation for biennial mammography for average risk women 50-74 years old
  - Grade “C” recommendation for mammography for average risk women 40-49 years old

Background

- Digital breast tomosynthesis (DBT), sometimes referred to as three-dimensional (3-D) mammography:
  - Multiple X-ray images of thin breast sections, compared to one image from conventional digital mammography (DM)
  - First DBT system was approved by the U.S. Federal Drug Administration in 2011
  - DBT seeks to improve mammography by improving cancer detection and reducing false-positive rate
  - In September, HTAS requested an evidence search for newer observational trials concurrent with public comment period

Scope Statement

- Population: Women between the ages of 40 and 74 years referred for breast cancer screening. Excludes women with history of:
  - Breast cancer
  - Clinically significant BRCA gene mutations
  - Li-Fraumeni syndrome
  - Cowden syndrome
  - Hereditary diffuse gastric cancer or other familial breast cancer syndromes
  - High-risk lesions (ductal or lobular carcinoma in situ, atypical ductal or lobular hyperplasia)
  - Previous large doses of chest radiation therapy (≥ 20 Gy) before age 30 years

Scope Statement

- Intervention: DBT (3-D mammography) in conjunction with standard 2-D digital mammography
- Comparator: Standard 2-D mammography with or without computer-aided diagnosis
- Outcomes:
  - All-cause mortality (critical outcome)
  - Breast cancer morbidity (critical outcome)
  - Test performance characteristics (important outcome)
  - Cancer stage at diagnosis (important outcome)
  - Recall rate/false-positive test results (important outcome)

Public Comments

- Comment: There are new observational trials and economic analyses since last systematic review
  - *New observational trials added to the evidence considered in the Coverage Guidance*
- Comment: Recall rates are lower in Europe than the U.S., so it is most appropriate to consider only U.S. studies to understand effects on recall rates
  - *Location of studies was specified in the Coverage Guidance, and a table with only U.S. studies was added*

Public Comments

- Comment: Evidence of reduced all-cause mortality or breast cancer morbidity should not be required to show that DBT is improvement over 2-D mammogram
  - *DBT's use as a primary screening modality should be subject to the normal evidentiary standards for screening tests; large-scale screening trials often report on all-cause and cancer-specific mortality*

Evidence Sources

- 4 recent, high-quality systematic reviews of observational trials of DBT+DM compared to DM alone
- 6 observational trials published since that last systematic review
- 3 economic analyses published recently
- No randomized controlled trials of DBT have been published, although several are currently underway

Evidence Review

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*
All-cause mortality *(Critical outcome)*	No data
Breast cancer morbidity *(Critical outcome)*	No data
Breast cancer stage at diagnosis *(Important outcome)*	No data

Evidence Review

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*
Test performance characteristics *(Important outcome)*	***Sensitivity for Breast Cancer*** Italian study DBT+DM*:* 0.85 (95% CI 0.74 to 0.92) DM: 0.54 (95% CI 0.42 to 0.65) U.S. study *DBT+DM:* 0.909 DM: 0.906 OR for improved sensitivity 1.03 (95% CI 0.57 to 1.89) ●○○○ *(Very low confidence)*

Evidence Review

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*
Test performance characteristics *(Important outcome)*	***Specificity for Breast Cancer*** <u>Italian study</u> DBT+DM: 0.97 (95% CI 0.96 to 0.98) DM: 0.96 (95% CI 0.95 to 0.97) <u>U.S. Study</u> DBT+DM: 0.913 DM: 0.897 OR for improved specificity 1.22 (95% CI 1.16 to 1.28) ●○○○ *(Very low confidence)*

Evidence Review

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*
Test performance characteristics *(Important outcome)*	***Cancer Detection Rate*** *DBT+DM: 4.6 to 8.9 per 1,000* *DM: 3.5 to 6.3 per 1,000* *Incremental cancer detection rate with DBT in U.S.-based studies:* -0.8 to 1.9 per 1,000 (11 studies, 5 with statistically significant increases in incremental cancer detection rate) ●●○○ *(Low confidence)*

Evidence Review

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*
Test performance characteristics *(Important outcome)*	***Cancer Detection Rate*** ***For women with dense breasts*** Incremental cancer detection rate with DBT: 1.4 per 1,000 (95% CI 0.9 to 2.0) in retrospective studies 3.9 per 1,000 (95% CI 2.7 to 5.1) in prospective studies ●●○○ *(Low confidence)*

Evidence Review

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*
Recall rate/False-positive rate *(Important outcome)*	**Recall rate** DBT+DM: 36 to 136 per 1,000 DM: 42 to 162 per 1,000 Change in recall rate with DBT in U.S.-based studies: -1.2% to -7.2% (11 studies, all with statistically significant results) *For women with dense breasts* Recall reduction with DBT of 23.3 per 1,000 (95% CI 16.8 to 29.9) ●●○○ *(Low confidence)*

Evidence Review

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*
Recall rate/False-positive rate *(Important outcome)*	**Biopsy Rate** *DBT+DM: 12 to 27 per 1,000* *DM: 14 to 22 per 1,000* **PPV Recall** *DBT+DM: 4.6% to 29.1%* *DM: 3.0% to 28.5%* **PPV Biopsy** *DBT+DM: 22.7% to 50%* *DM: 16.7% to 30.2%* ●●○○ *(Low confidence)*

Evidence Review

DBT+DM over DM alone in U.S.-based studies

Study	Incremental Cancer Detection Rate	Change in Recall Rate
Haas (2013)	0.5 per 1,000 (NS)	-3.6%
Rose (2013)	1.4 per 1,000 (NS)	-3.2%
Destounis (2014)	1.6 per 1,000 (NR)	-7.2%
Friedewald (2014)	1.2 per 1,000	-1.7%
Greenberg (2014)	1.4 per 1,000	-2.6%
Lourenco (2014)	-0.8 per 1,000 (NS)	-2.9%
McCarthy (2014)	0.9 per 1,000 (NS)	-1.6%
Rose (2014)	1.9 per 1,000	-2.8%
Conant (2016)	1.5 per 1,000	-2.3%
McDonald (2016)	1.5 per 1,000 (NS)	-1.2%
Sharpe (2016)	1.9 per 1,000	-1.4%

Evidence Summary

- Evidence for DBT is limited to observational studies, most of which have methodological limitations and inadequate follow-up periods
- Effects of DBT on all-cause mortality, breast cancer morbidity, and breast cancer stage at diagnosis are unknown
- Two studies with adequate follow-up to ascertain interval cancer rates reached differing conclusions
  - One study showed increased sensitivity and similar specificity
  - One study showed identical sensitivity and improved specificity

Evidence Summary

- Low-quality evidence with mixed results that DBT+DM improves cancer detection rates
- Low-quality evidence that DBT+DM reduces recall rates, particularly when limited to U.S.-based studies
- There are no meta-analytic estimates available for any of the outcomes, except for women with dense breasts

Guidelines

- U.S Preventive Services Task Force (2016):
  - Grade “I” statement for DBT, concluding that there was insufficient evidence to assess the benefits and harms of DBT
  - Grade “I” statement for adjunctive or supplemental screening, including DBT, for women with dense breasts

Guidelines

- Current evidence is insufficient to assess effectiveness of DBT:
  - American Congress of Obstetricians and Gynecologists
  - American Cancer Society
  - American College of Physicians
  - American Academy of Family Physicians
- National Comprehensive Cancer Network: recently added, "consider tomosynthesis"
- American College of Radiology: DBT is no longer investigational and has demonstrated improvement in outcomes compared to DM

Policy Landscape

- Washington Medicaid covers DBT when performed with screening mammography for patients aged 40 to 74 who are candidates for screening mammography
- Reviewed four private payers:
  - Aetna, Moda, and Regence do not cover DBT because of insufficient evidence for its effectiveness
  - Cigna covers DBT

HTAS Decision on Coverage Guidance

Digital breast tomosynthesis for breast cancer screening in average risk women is not recommended for coverage (*weak recommendation*).

HTAS Rationale

- It is likely that DBT decreases recall rates as compared with DM alone, based on observational studies performed in the US
- We have low confidence that DBT improves cancer detection rates.
- We are not confident that any improvement in cancer detection rates with DBT, if clearly demonstrated, would result in cancers being detected at earlier stages, leading to earlier intervention that improves clinical outcomes.

HTAS Rationale

- Adding DBT to standard DM adds cost, and we are not confident that DBT is cost-effective, based on current analysis.
- Randomized controlled trials are currently underway that should help with greater understanding of the risks and benefits of DBT+DM, including the critical issue of whether DBT improves clinical outcomes.
- The recommendation against coverage is a weak recommendation because further evidence could change the recommendation.

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: DIGITAL BREAST TOMOSYNTHESIS (3D MAMMOGRAPHY) FOR BREAST CANCER SCREENING IN AVERAGE RISK WOMEN

For VbBS/HERC Meeting Materials 2/2/2017

HERC Coverage Guidance

Digital breast tomosynthesis for breast cancer screening in average risk women is not recommended for coverage *(weak recommendation).*

Note: Definitions for strength of recommendation are provided in Appendix A *GRADE Informed Framework Element Description*.

RATIONALE FOR DEVELOPMENT OF COVERAGE GUIDANCES AND MULTISECTOR INTERVENTION REPORTS

Coverage guidances are developed to inform coverage recommendations for public and private health plans in Oregon as they seek to improve patient experience of care, population health, and the cost-effectiveness of health care. In the era of the Affordable Care Act and health system transformation, reaching these goals may require a focus on population-based health interventions from a variety of sectors as well as individually focused clinical care. Multisector intervention reports will be developed to address these population-based health interventions or other types of interventions that happen outside of the typical clinical setting.

The HERC selects topics for its reports to guide public and private payers based on the following principles:

- Represents a significant burden of disease or health problem
- Represents important uncertainty with regard to effectiveness or harms
- Represents important variation or controversy in implementation or practice
- Represents high costs or significant economic impact
- Topic is of high public interest

Our reports are based on a review of the relevant research applicable to the intervention(s) in question. For coverage guidances, which focus on clinical interventions and modes of care, evidence is evaluated using an adaptation of the GRADE methodology. For more information on coverage guidance methodology, see Appendix A.

Multisector interventions can be effective ways to prevent, treat, or manage disease at a population level. For some conditions, the HERC has reviewed evidence and identified effective interventions, but has not made coverage recommendations, as many of these policies are implemented in settings beyond traditional health care delivery systems.

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 several 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. Estimates of effect are derived from the evidence presented in this document. The level of confidence in the estimate is determined by the Commission based on the assessment of two independent reviewers from the Center for Evidence-based Policy. Unless otherwise noted, estimated resource allocation, values and preferences, and other considerations are assessments of the Commission.

Coverage question: Should digital breast tomosynthesis (DBT) be recommended for coverage for breast cancer screening?				
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***	**Resource allocation**	**Values and Preferences**	**Other considerations**
All-cause mortality *(Critical outcome)*	No data	Based on Medicare fee-for-service fee schedules, DBT increases the cost of mammography by 41%. While the cost of DBT in addition to DM is relatively modest at an individual level, this would add significant costs at the population level due to the large number of people electing breast cancer screening. If DBT+DM leads to lower rates of recall and/or detects	Women would strongly value having a test that is precise in that it detects cancer that will impact future morbidity and mortality, but would also decrease their risk of unnecessary worry and procedures. If a test is much more likely to pick up a cancer, they would strongly favor it if they know it will affect their long-term outcomes. There would be significant variability in	
Breast cancer morbidity *(Critical outcome)*	No data			
Test performance characteristics *(Important outcome)*	*Sensitivity for Breast Cancer:* Italian study DBT+DM: 0.85 (95% CI 0.74 to 0.92) DM: 0.54 (95% CI 0.42 to 0.65) U.S. study DBT+DM: 0.9096 DM: 0.9069 OR for improved sensitivity 1.03 (95% CI 0.57 to 1.89)			

Coverage question: Should digital breast tomosynthesis (DBT) be recommended for coverage for breast cancer screening?				
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***	**Resource allocation**	**Values and Preferences**	**Other considerations**
	Specificity for Breast Cancer: <u>Italian study</u> DBT+DM: 0.97 (95% CI 0.96 to 0.98) DM: 0.96 (95% CI 0.95 to 0.97) <u>U.S. study</u> DBT+DM: 0.913 DM: 0.897 OR for improved specificity 1.22 (95% CI 1.16 to 1.28) ●○○○ *(Very low confidence)* *Cancer Detection Rate:* DBT+DM: 4.6 to 8.9 per 1,000 DM: 3.5 to 6.3 per 1,000 *Incremental cancer detection rate with DBT in U.S.-based studies:* -0.8 to 1.9 per 1,000 (11 studies, 5 with statistically significant increases in incremental cancer detection rate) ●●○○ *(Low confidence)* *For women with dense breasts, incremental cancer detection rate with DBT:* 1.4 per 1,000 (95% CI 0.9 to 2.0) in retrospective studies and 3.9 per 1,000 (95% CI 2.7 to 5.1) in prospective studies ●●○○ *(Low confidence)*	cancer at an earlier stage, leading to improved outcomes, these costs could be offset.	how women would value an increased risk of a false-positive test and the subsequent need for biopsy or recall compared to a possible missed cancer diagnosis, but we assume that many women would have a strong preference to avoid a missed cancer diagnosis.	

Coverage question: Should digital breast tomosynthesis (DBT) be recommended for coverage for breast cancer screening?				
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***	**Resource allocation**	**Values and Preferences**	**Other considerations**
Breast cancer stage at diagnosis *(Important outcome)*	No data			
Recall rate/False-positive rate *(Important outcome)*	*Recall rate:* DBT+DM: 36 to 136 per 1,000 DM: 42 to 162 per 1,000 *Change in recall rate with DBT in U.S.-based studies:* -1.2% to -7.2% (11 studies, all with statistically significant results) *Biopsy rate:* DBT+DM: 12 to 27 per 1,000 DM: 14 to 22 per 1,000 *PPV Recall:* *DBT+DM: 4.6% to 29.1%* *DM: 3.0% to 28.5%* *PPV Biopsy:* DBT+DM: 22.7% to 50% DM: 16.7% to 30.2% ●●○○ *(Low confidence)*			

Coverage question: Should digital breast tomosynthesis (DBT) be recommended for coverage for breast cancer screening?				
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***	**Resource allocation**	**Values and Preferences**	**Other considerations**
	For women with dense breasts: Recall reduction with DBT of 23.3 per 1,000 (95% CI 16.8 to 29.9) ●●○○ *(Low confidence)*			
Balance of benefits and harms: There may or may not be a benefit in terms of cancer detection rate. There does appear to be an improvement in the recall rate. There are no clear harms, unless the possible increased cancer detection rate is mostly due to the detection of indolent and non-invasive lesions.				
Rationale: ~~We are uncertain of the effectiveness of DBT+DM versus DM based on the absence of studies evaluating the critical outcomes, and have very low confidence on the impact of DBT on the important outcomes (based on studies with conflicting results). Adding DBT to standard DM adds cost, with insufficient evidence that it improves any outcome. Additionally, randomized controlled trials are currently underway that should help with greater understanding of the risks and benefits of DBT+DM. The recommendation against coverage is a weak recommendation because further evidence could change the recommendation.~~ Based on observational studies performed in the US, it is likely that DBT decreases recall rates as compared with DM alone. We have low confidence that DBT improves cancer detection rates. We are also not confident that any improvement in cancer detection rates with DBT, if clearly demonstrated, would result in cancers being detected at earlier stages, leading to earlier intervention that improve clinical outcomes. Adding DBT to standard DM adds cost, and we are not confident that DBT is cost-effective, based on current analysis. Additionally, randomized controlled trials are currently underway that should help with greater understanding of the risks and benefits of DBT+DM, including the critical issue of whether DBT improves clinical outcomes. The recommendation against coverage is a weak recommendation because further evidence could change the recommendation.				
Recommendation: Digital breast tomosynthesis for breast cancer screening is not recommended for coverage *(weak recommendation).*				

Note: GRADE framework elements are described in Appendix A. The Quality of Evidence rating was assigned based on the GRADE Evidence Profile found in Appendix B.

EVIDENCE OVERVIEW

Clinical Background

Approximately 1 in 8 (12%) women in the United States develop invasive breast cancer during their lifetime, making breast cancer the second most common cancer (following skin cancer) in American women (American Cancer Society [ACS], 2016c). In 2013, there were 230,815 breast cancer diagnoses and 40,860 breast cancer deaths in women in the United States (Centers for Disease Control and Prevention [CDC], 2016a). In men, breast cancer is relatively rare, accounting for an additional 2,109 breast cancer diagnoses and 464 breast cancer deaths in 2013.

Trends in breast cancer incidence and mortality reveal health disparities across race and ethnicity. The rate of breast cancer diagnoses has remained stable in white women over the last decade, while increasing slightly in African American women (ACS, 2016c). The breast cancer mortality rate overall has steadily declined since 1989, but this trend disproportionately represents a larger decrease in breast cancer deaths among white women compared to other races and ethnicities (CDC, 2012). African American women are 40% more likely to die of breast cancer than white women, which reflects the need for more timely follow-up and improved access to high-quality treatment following a positive screening in this population.

Indications

The declining breast cancer mortality rate in the United States is partially attributed to greater screening efforts and thus earlier detection, in addition to fewer women using hormone therapy after menopause and improved quality of treatment (ACS, 2016c). Screening technology, such as mammography, can identify cancer at an earlier stage, before an individual experiences symptoms (ACS, 2016b). When detected early, abnormal tissue or cancer is easier to treat and patients have better outcomes. Women diagnosed with breast cancer in earlier stages have higher relative five-year survival rates (ACS, 2016a). The five-year survival rate for women with Stage 0 or Stage I breast cancer in the United States is almost 100%, compared to 22% for women with Stage IV breast cancer.

A systematic review and meta-analysis of randomized controlled screening trials for breast cancer completed in 2016 to inform the U.S. Preventive Services Task Force (USPSTF) concluded that screening mammography reduces breast cancer mortality, but not all-cause mortality (Nelson et al., 2016b). The absolute reduction in breast cancer mortality afforded by screening mammography varies by age group; for women 39-49 years old screening prevents 3 breast cancer deaths per 10,000 women over 10 years (a finding that was not statistically significant), while in women aged 60-69 years screening prevent 21 deaths per 10,000 women screened over 10 years. The review also concluded that the rate of false-positive recall from screening mammography is high: the cumulative rate of false-positive recalls over 10 years was 61% among women undergoing annual screening and 42% for women receiving biennial screening. On the basis of this review, the USPSTF offered a B recommendation to biennial mammography for average risk women between the ages of 50-74 years and a C recommendation for screening mammography for women 40-49 years old. The USPSTF issued an I recommendation to digital breast tomosynthesis.

The benefits of screening generally increase with age: the greatest benefit is for women aged 50 to 74 (U.S. Preventative Services Task Force, 2016). However, screening recommendations vary by individual case and risk level. Multiple factors contribute to individual risk aside from being female, including age, genetic mutations, denser breasts, family history of breast cancer, physical inactivity, and alcohol consumption (CDC, 2016b).

Advocates of DBT+DM generally recommend it to reduce false-positives and increase cancer detection rate.

Technology Description

Digital breast tomosynthesis (DBT), sometimes referred to as three-dimensional (3-D) mammography, is a breast cancer screening technique that was developed to improve detection and characterization of abnormal tissue in the breasts, especially in women with denser breasts (Helvie, 2011). DBT provides multiple X-ray images of thin breast sections, which can potentially reveal cancers concealed by normal tissue. An X-ray tube moves in an arc around a patient's compressed breast, which allows exposures from different angles to create a series of images. The image dataset is reconstructed into multiple images using mathematical algorithms and then reviewed by a radiologist. This process is distinct from standard (two-dimensional or 2-D) digital mammography (DM), in which only one image of overlapping tissue is produced. The first DBT system was approved by the U.S. Federal Drug Administration (FDA) on February 11, 2011 (U.S. FDA, 2015).

Key Questions and Outcomes

The following key questions (KQ) guided the evidence search and review described below. For additional details about the review scope and methods, please see Appendix C.

1. What is the comparative effectiveness of DBT as a primary screening modality in women referred for breast cancer screening?
2. Does the comparative effectiveness of DBT vary by the following characteristics:
    a. Age
    b. Race or ethnicity
    c. Breast density
3. In a screening population, how do the test characteristics of 3-D/2-D mammography compare to those of standard 2-D mammography?
4. What are the harms of 3-D/2-D mammography compared to standard 2-D mammography alone?
5. If DBT is used as a primary screening modality, what is the optimal screening interval, and does that interval vary according to the characteristics listed in Key Question 2?

Critical outcomes selected for inclusion in the GRADE table are all-cause mortality and breast cancer morbidity. Important outcomes selected for inclusion in the GRADE table are test performance characteristics, cancer stage at diagnosis, and recall rate/false-positive test results.

Evidence Review

No randomized controlled trials of DBT have been published, although several are currently underway. Staff identified four recent, high-quality systematic reviews of observational trials of DBT combined with DM compared to DM alone. The included systematic reviews are summarized in Table 1.

Table 1. Summary of Included Systematic Reviews

Citation, Study Details	Center QA	# of Studies (k), Population (n)	Study Summary and Findings	Comments
Melnikow (2016a) Search Dates January 2000 to October 2015 Included Study Designs Prospective cohort	Good	k = 1 total n = 7,292 *SR's quality assessment of individual study:* Good	Comparators DBT + DM vs. DM Outcomes *Sensitivity for Breast Cancer:* 0.85 (95% CI, 0.74 to 0.92) vs. 0.54 (95% CI, 0.42 to 0.65) *Specificity for Breast Cancer:* 0.97 (95% CI, 0.96 to 0.98) vs. 0.96 (95% CI, 0.95 to 0.97)	Included studies Ciatto et al., (2013), Houssami et al. (2014) (2 reports from the same study - STORM) Summarized in evidence tables[1] Destounis et al., (2014), Friedewald et al., (2014), Greenberg et al., (2014), Haas et al., (2013), Lang et al., (2015), McCarthy et al., (2014), Rose et al., (2013), Skaane et al., (2013a)
Nelson (2016a) Search Dates Through December 2014 Included Study Designs SRs, RCTs, observational studies	Good	k=5 total n = 517,011 *SR's quality assessment of individual studies:* Poor	Comparators DBT + DM vs. DM Outcomes *Recall Rate*: Significantly lower for DBT+ DM vs. DM across studies One U.S. study reported 16 fewer recalls per 1,000 screens (p<0.001) (Friedewald et al., 2014)	Included studies Ciatto et al., (2013), Friedewald et al., (2014), Haas et al., (2013), Rose et al., (2013), Skaane et al., (2013a) Evidence limited by lack of RCTs, comparability of results not reported, and outcomes not reported uniformly

[1] These studies did not meet the inclusion criterion of describing test performance characteristics, but were included in evidence tables to illustrate more proximal outcomes.

Citation, Study Details	Center QA	# of Studies (k), Population (n)	Study Summary and Findings	Comments
			Biopsy Rate: Increase of 1.3 biopsies per 1,000 screens for DBT+ DM compared to DM (p<0.001) (Friedewald et al., 2014)	
WA HTA (2014) Search Dates January 1990 to November 2014 Included Study Designs Observational studies	Good	k = 9 total n = 313,298 *SR's quality assessment of individual studies:* Poor	Comparators DBT+ DM vs. DM Outcomes* *Cancer Detection Rate (CDR):* 4 to 6 / 1,000 vs. 3 to 5/1,000 *Recall Rate:* 80 to 140/1,000 vs. 100 to 160/1,000 *Biopsy Rate:* 12 to 27/1,000 vs. 14 to 22/1,000 *PPV Biopsy:* 25 to 30% vs. 20 to 25% *Meta-analysis not performed for outcomes, significance not reported	Included studies Ciatto et al., (2013), Destounis et al., (2014), Friedewald et al., (2014), Greenberg et al., (2014), Haas et al., (2013), Lourenco et al., (2014), McCarthy et al., (2014), Rose et al., (2013), Skaane et al., (2013a), Skaane et al., (2013b) All included articles were rated by the review authors as poor quality due to insufficient follow-up in all but one study, and a 20% dropout rate in the study with 12-month follow-up (Destounis et al., 2014) Some of the studies had possible selection bias Authors reported a moderate to high degree of uncertainty in recall rate, biopsy rate, and CDR There is a low to moderate degree of uncertainty for the PPV of biopsy

Citation, Study Details	Center QA	# of Studies (k), Population (n)	Study Summary and Findings	Comments
Melnikow (2016b) Search Dates January 2000 to July 2015 Included Study Designs Observational studies	Good	k = 4 total n = 30,195 *SR's quality assessment of individual studies:* Fair	Comparators DBT+DM vs. DM for screening women with dense breasts Outcomes* *Cancer Detection Rate (CDR):* 5.4 to 6.9 / 1,000 vs. 4.0 to 5.2 / 1,000 *Recall Rate:* 7% to 11% vs. 9% to 17% *Reported ranges, meta-analysis not performed	Included studies Ciatto et al., (2013), Haas et al., (2013), McCarthy et al., (2014), Rose et al., (2013) The 3 U.S. studies were single-site retrospective designs, and one study included women at above-average risk
Houssami (2016) Search Dates January 200 to July 2016 Included Study Designs Retrospective and prospective cohorts	Good	k = 8 total n = 291,232	Comparators DBT+DM vs. DM for screening women with dense breasts Outcomes *Incremental Cancer Detection Rate (CDR):* 1.4 to 3.9 more cancers detected per 1,000 with DBT+DM *Recall Rate Reduction:* 23.3 fewer recalls per 1,000 with DBT+DM	Ciatto, et al., (2013), Lang, et al., (2016), Bernardi, et al., (2016), Tagliafico, et al., (2016), Rose, et al., (2013), McCarthy, et al., (2014), Conant, et al., (2016), Rafferty, et al., (2016)

EVIDENCE SUMMARY

Key Questions 1 and 3

What is the comparative effectiveness of digital breast DBT as a primary screening modality in women referred for breast cancer screening?

In a screening population, how do the test characteristics of 3D/2D mammography compare to those of standard 2D mammography?

Melnikow et al., 2016a

A good-quality systematic review of DBT for breast cancer screening conducted for the Agency for Health Research and Quality (AHRQ) was published in January 2016 (Melnikow et al., 2016a). The systematic review included articles published between January 2000 and October 2015 that reported on the test performance of DBT in a screening population (asymptomatic women 40 years of age or older) compared to a comprehensive reference standard that was applied to all test results. The authors of the systematic review required that studies report one year of clinical follow-up after the initial imaging in order to ascertain interval breast cancers that were not detected during screening.

Only a single study met the inclusion criteria. That study, known as the Screening with Tomosynthesis OR standard Mammography (STORM) trial (Houssami et al., 2014), included a prospective cohort of more than 7,000 women aged 48 years or older from northern Italy. These women had both DM and DBT performed at the time of screening. Sequential reading was performed by eight radiologists who read the DM first, then interpreted the combined DM and DBT images. Median follow-up after screening was approximately 20 months. Among this cohort, 63 women were diagnosed with 65 breast cancers during the follow-up period. The authors of the AHRQ review reported the test characteristics from the single-reader analysis because they considered it the most consistent with the practice in the United States. DBT combined with DM (DBT+DM) was more sensitive than DM alone (85% vs. 54%). The two tests had similar specificity (97% for DBT+DM vs. 96% for DM). Overall cancer detection rates were 7.4 per 1,000 for DBT+DM compared to 4.8 per 1,000 for DM. Overall recall rates were 3.6% for DBT+DM compared to 4.2% for DM alone.

The authors of the AHRQ review summarized the results of eight additional screening cohort studies that did not report on test performance, but did report on cancer detection rates, recall rates, and biopsy rates. The authors did not methodologically assess the additional studies, and the results were only summarized in an included evidence table. Overall, the authors concluded that in most studies DBT was associated with increased cancer detection rates, reduced recall rates, and higher positive predictive value for initial recall. The results from the additional trials were mixed with respect to detection of invasive cancers and biopsy rate.

Nelson et al., 2016

A good-quality systematic review of the harm of breast cancer screening, including a comparison of the harms associated with different screening modalities, was published in 2016 to inform the deliberations of the U.S. Preventive Services Task Force (Nelson et al., 2016). The authors included cohort studies performed in asymptomatic populations. The authors assessed the overall quality of the evidence for differential harm by screening modality as poor, noting the absence of randomized trials, the failure to report group characteristics at baseline, and inconsistency in the reporting of outcomes including biopsy rate. Four of the five trials found lower recall rates with DBT+DM compared to DM, and the fifth trial found no significant difference. Only one of the trials reported on biopsy rate and found a statistically significant difference of 1.3 fewer biopsies per 1,000 for DM compared with DBT+DM.

Washington Health Technology Assessment, 2014

A good-quality systematic review of DBT for breast cancer screening was included in a Washington Health Technology Assessment (WA HTA) report released in December 2014 (WA HTA, 2014). The authors included nine studies reported in 10 articles and deemed all of the included studies to be of poor methodological quality. Issues of study heterogeneity prevented a formal meta-analysis, but the authors provided estimations of the cancer detection rate, recall rate, biopsy rate, and positive predictive value of biopsy between the DM and DBT+DM groups. Those results are summarized in Table 2.

Table 2. Summary Comparison of DM and DBT+DM from the WA HTA report

Outcome	DM	DBT+DM	Uncertainty
Cancer detection rate (per 1,000)	3–5	4–6	Moderate-high
Recall rate (per 1,000)	100–160	80–140	Moderate-high
Biopsy rate (per 1,000)	14–22	12–27	Moderate
Positive predictive value of biopsy	20–25%	25–30%	Low-moderate

Melnikow et al., 2016b

A good-quality systematic review of supplemental breast cancer screening for women with dense breasts, including DBT, was published in 2016 (Melnikow et al., 2016b). The authors included four fair-quality studies of DBT+DM compared to DM alone in women with dense breasts. The three U.S. studies were single retrospective cohorts comparing outcomes before and after implementation of DBT. None of the included studies reported on test performance characteristics. Three of the studies reported on cancer detection rate (4.0–5.2 per 1,000 for DM compared to 5.4–6.9 per 1,000 for DBT+DM); one of the studies reported that the rate of invasive cancers was the same between the two groups. Among the three U.S. studies included, recall rates were lower for DBT+DM (7%–11%) compared to DM (9%–17%). The authors noted that there is no reference standard by which to measure the accuracy of BI-RADS density determinations and that reclassification of breast density on sequential exams is common.

Results from individual studies included in the systematic reviews or submitted in public comments are summarized in Table 3, and Table 4 summarizes the U.S.-based studies.

Table 3. Results from Individual Studies Included in the Systematic Reviews or Submitted in Public Comment

Author (Year) Study Size Location	Source QA	Study Design and Population Characteristics	CDR per 1,000 women (% invasive)	Recall Rate (%)	PPV Recall	PPV Biopsy	Comments
Ciatto (2013) n = 7,292 Italy	Poor (WA HTA, 2014)	Prospective cohort (one arm) Population-based screening centers Mean age: 58 Test: Selenia Dimensions, Hologic	DBT+DM: 8.1 DM: 5.3 (p<0.0001)	DBT+DM: 4.3% DM: 5% (NS)	NR	NR	No long-term follow-up; one abnormal read-flagged recall
Destounis (2014)	Poor (WA HTA, 2014)	Retrospective cohort (two arm)	DBT+DM: 5.4 (33%) DM: 3.8 (50%)	DBT+DM: 4.2% DM: 11.4%	NR	DBT+ DM: 50.0% DM: 16.7%	One-year follow-up; 80% completion rate

Author (Year) Study Size Location	Source QA	Study Design and Population Characteristics	CDR per 1,000 women (% invasive)	Recall Rate (%)	PPV Recall	PPV Biopsy	Comments
DBT = 524 DM = 524 New York		Community breast clinic Mean age: 59 Test: Selenia Dimensions, Hologic SecurView, Hologic	(sig. NR)	(p<0.0001)		(sig. NR)	Selection bias likely due to baseline risk factors for breast cancer or abnormal imaging in the DBT group; some participants had a personal history of breast cancer
Friedewald (2014) DBT+DM exams = 173,663 DM exams = 281,187 U.S., multistate	Poor (WA HTA, 2014)	Retrospective cohort (two arm): Pre-post 13 academic medical centers and breast diagnostic/screening centers Mean age: 56.2 for DBT+DM; 57.0 for DM Test: Selenia Dimensions, Hologic	DBT+DM: 5.5 (75%) DM: 4.3 (67%) (p<0.001)	DBT+DM: 8.9% DM: 10.6% (p<0.001)	DBT+DM: 6.1% DM: 4.1% (p<0.0001)	DBT+DM: 29.2% DM: 24.2% (p<0.001)	Insufficient follow-up Pre-post design No individual-level data to stratify populations The biopsy rate was higher for DBT+DM group: 1.9% vs. 1.8% (p=0.004)
Greenberg (2014)	Poor (WA HTA, 2014)	Retrospective cohort (two arm)	DBT+DM: 6.3 (74%) DM: 4.9 (62%)	DBT+DM: 13.6% DM: 16.2% (p<0.0001)	DBT+DM: 4.6% DM: 3.0% (p=0.0003)	DBT+DM: 22.7% DM: 21.5% (NS)	No follow-up Volunteer bias possible

Author (Year) Study Size Location	Source QA	Study Design and Population Characteristics	CDR per 1,000 women (% invasive)	Recall Rate (%)	PPV Recall	PPV Biopsy	Comments
DBT+DM exams = 20,943 DM exams = 38,674 Washington, D.C.		Community-based multisite radiology practice Mean age: 59.5 Test: Selenia Dimensions, Hologic	(p=0.035)				May have overlap with Friedewald (2014) DBT+DM group had higher biopsy rate (2.6% vs. 2.1%, p=0.0003)
Haas (2013) DBT+DM = 6,100 DM = 7, 058 Connecticut	Poor (WA HTA, 2014)	Retrospective cohort (two arm) Mean age: 56 Test: Selenia Dimensions, Hologic	DBT+DM: 5.7 (69%) DM: 5.2 (68%) (NS)	DBT+DM: 8.4% DM: 12.0% (p<0.01)	DBT+DM: 6.8% DM: 4.3%[2]	NR	No follow-up Women in DBT group had increased risk factors for breast cancer at baseline
Houssami (2014) n = 7,292	Good (Melnikow, 2016a)	Prospective cohort (one arm)	DBT+DM: 7.4 DM: 4.8 (p<0.001)	DBT+DM: 3.6% DM: 4.2% (NS)	DBT+DM: 21% DM: 11%[3]	NR	Follow-up 13 months or greater Screen positive if one of two readers

[2] Center staff calculated this by dividing cancers detected by the product of the recall rate and the number of exams, significance not reported.
[3] Drawn from AHRQ (2016) report; PPV not reported in original study. Significance not recorded.

Author (Year) Study Size Location	Source QA	Study Design and Population Characteristics	CDR per 1,000 women (% invasive)	Recall Rate (%)	PPV Recall	PPV Biopsy	Comments
Italy		Population screening program Median age: 58 Test: Selenia Dimensions, Hologic					interpreted DM or DBT as abnormal
Lourenco (2014) DBT exams = 12,921 DM exams = 12,577 U.S.	Poor (WA HTA, 2014)	Retrospective cohort (two arm) Single breast imaging center Mean age: 55.3 DBT, 54.6 DM Test: Selenia Dimensions, Hologic	DBT: 4.6 DM: 5.4 (NS)	DBT: 6.4% DM: 9.3% (p<0.00001)	DBT: 7.2% DM:5.8% (NS)	DBT: 23.8% DM: 30.2% (sig. NR)	Insufficient follow-up Pre-post design Biopsy rate 1.7% DBT+DM vs. 1.6% DM (stat dif NR)
McCarthy (2014) DBT+DM exams = 15,571	Poor (WA HTA, 2014)	Cohort (two arm) One academic medical center Mean age: 57	DBT+DM: 5.5 (71%) DM: 4.6 (69%) (NS)	DBT+DM: 8.8% DM: 10.4% (p<0.001)	DBT+DM: 6.2% DM: 4.4% (p=0.05)	DBT+DM: 25.7% DM: 24.7% (NS)	Insufficient follow-up Overlap with Friedewald (2014) Pre-post design

Author (Year) Study Size Location	Source QA	Study Design and Population Characteristics	CDR per 1,000 women (% invasive)	Recall Rate (%)	PPV Recall	PPV Biopsy	Comments
DM exams = 10, 728 Pennsylvania		Test: Selenia Dimensions, Hologic					Biopsy rate for DBT+ DM 2.0% vs. 1.8%, for DM (NS)
Rose (2013) DBT+DM exams = 9,499 DM exams = 13,856 Texas	Poor (WA HTA, 2014)	Cohort (two arm) Multisite, community-based Mean age: NR Test: Selenia Dimensions, Hologic	DBT+DM: 5.4 (80%) DM: 4.0 (70%) (NS)	DBT+DM: 5.5% DM: 8.7% (p<0.001)	DBT+DM: 10.1% DM: 4.7% (p<0.001)	DBT+DM: 39.8% DM: 26.5% (p=0.06)	No follow-up Pre-post design Biopsy rate 1.1% DBT + DM vs. 1.5% DM (NS)
Skaane (2013a) n = 12, 621 exams Norway	Poor (WA HTA, 2014)	Prospective cohort (one arm) Citywide screening program	DBT+DM: 8.0 (80%) DM: 6.1 (73%) (p=0.001)	DBT+DM: 6.1% DM: 6.7% (p<0.001)	DBT+DM: 29.1% DM: 28.5% (NS)	NR	Incomplete follow-up Independent double-reading with

Author (Year) Study Size Location	Source QA	Study Design and Population Characteristics	CDR per 1,000 women (% invasive)	Recall Rate (%)	PPV Recall	PPV Biopsy	Comments
		Mean age: NR Test: Selenia Dimensions, Hologic					arbitration prior to recall CDR and recall rate calculated for each image prior to arbitration
Skaane (2013b) n = 12, 621 exams Norway	Poor (WA HTA, 2014)	Prospective cohort (one arm) Citywide screening program Mean age: 59.3 Test: Selenia Dimensions, Hologic	DBT+DM: 9.4 DM: 7.1 (p<0.001)	DBT+DM: 3.7% DM: 2.9% (p<0.001)	DBT+DM: 24.7% DM: 25.5% (NS)	NR	Incomplete follow-up Independent double-reading with arbitration prior to recall

Author (Year) Study Size Location	Source QA	Study Design and Population Characteristics	CDR per 1,000 women (% invasive)	Recall Rate (%)	PPV Recall	PPV Biopsy	Comments
Sharpe (2016) n = 85,852 exams United States	Poor	Retrospective cohort Single center Mean age: 57.6 Test: Selenia Dimensions, Hologic	DBT+DM: 5.4 DM: 3.5 (p<0.001) Invasive CDR DBT+DM: 2.81 DM: 2.46 (NS)	DBT+DM: 6.1% DM: 7.5% (p<0.001)	NR	NR	Baseline differences between cohorts Less experienced readers were excluded from recall rate analysis
Rose (2014) n = 10,878 United States	Poor	Retrospective reading study Single practice Mean age: NR Test: Selenia Dimensions, Hologic	DBT+DM: 5.4 (81%) DM: 3.5 (76%) (p<0.001)	DBT+DM: 5.4% DM: 8.2% (p<0.001)	NR	NR	Retrospective reading may influence interpretation

Author (Year) Study Size Location	Source QA	Study Design and Population Characteristics	CDR per 1,000 women (% invasive)	Recall Rate (%)	PPV Recall	PPV Biopsy	Comments
McDonald (2016) n = 44,468 United States	Poor	Retrospective cohort study Single center Mean age: 56.8 Test: Selenia Dimensions, Hologic	DBT+DM: 5.5 to 6.1 DM: 4.6 (NS)	DBT+DM: 8.8 to 9.2% DM: 10.4% (p<0.001)	DBT+DM: 6.2% to 6.7% DM: 4.4% (p=0.02)	Reported as not statistically significantly different (p=0.37)	
Lang (2016) n = 7,500 Sweden	Fair	Prospective cohort (one arm) Citywide screening program Mean age: 56 Test: Mammostat Inspiration, Siemens	DBT: 8.9 DM: 6.3 (p<0.0001)	DBT: 3.8% DM: 2.6% (p<0.0001)	DBT: 24% DM: 24% (NS)	NR	

Author (Year) Study Size Location	Source QA	Study Design and Population Characteristics	CDR per 1,000 women (% invasive)	Recall Rate (%)	PPV Recall	PPV Biopsy	Comments
Conant (2016) n = 142,883 United States	Poor	Retrospective cohort Three centers in the Northeast U.S. Mean age: NR Test: NR	DBT+DM 5.9 DM: 4.4 (p=0.0026) Invasive CDR DBT+DM: 4.4 DM: 3.3 (p=0.0449)	DBT+DM: 8.7% DM: 10.4% (p<0.0001)	DBT+DM: 6.4% DM: 4.1% (p<0.001)	NR	Baseline differences between cohorts
Bernardi (2016) n = 9,672 Northern Italy	Fair	Prospective double-reading study Population-based screening program in Italy Mean age: 58 Test: Selenia Dimensions, Hologic	DBT+DM: 8.8 DM: 6.3 (p<0.0001)	False-positive recall rate: DBT+DM 4.45% DM: 3.42% (p<0.0001)	NR	NR	Double reading model is uncommon in the U.S. Inadequate follow-up to detect interval cancers

Table 4. Incremental Cancer Detection Rate and Change in Recall Rate for DBT+DM over DM alone in U.S.-based studies

Study	Incremental Cancer Detection Rate	Change in Recall Rate
Haas (2013)	0.5 per 1,000 (NS)	-3.6%
Rose (2013)	1.4 per 1,000 (NS)	-3.2%
Destounis (2014)	1.6 per 1,000 (NR)	-7.2%
Friedewald (2014)	1.2 per 1,000	-1.7%
Greenberg (2014)	1.4 per 1,000	-2.6%
Lourenco (2014)	-0.8 per 1,000 (NS)	-2.9%
McCarthy (2014)	0.9 per 1,000 (NS)	-1.6%
Rose (2014)	1.9 per 1,000	-2.8%
Conant (2016)	1.5 per 1,000	-2.3%
McDonald (2016)	1.5 per 1,000 (NS)	-1.2%
Sharpe (2016)	1.9 per 1,000	-1.4%

All observed differences were statistically significant except where noted by NS (not significant) or NR (test of statistical significance not reported). For additional details, see Table 3.

Critical Outcome: All-cause mortality

None of the identified studies reported on the effects of DBT on all-cause mortality.

Critical Outcome: Breast cancer morbidity

None of the identified studies reported on the effects of DBT on breast cancer morbidity.

Important Outcome: Test performance characteristics

Only a single study from the included systematic reviews was designed to allow estimation of the test performance characteristics in a screening population (Houssami et al., 2014). In this prospective study of single-reader breast cancer detection that followed women for a median of nearly 20 months to detect interval cancers, the sensitivity of DBT+DM (0.85, 95% CI 0.74 to 0.92) was superior to that of DM (0.55, 95% CI 0.42 to 0.65). Specificity for DBT+DM was 0.97 (95% CI 0.96 to 0.98) compared to 0.96 (95% CI 0.95 to 0.98) for DM. As the AHRQ review authors noted, the observed sensitivity for DM in this study was well below that reported in other studies.

All 11 of the studies included in the systematic reviews reported on cancer detection rate. Five studies found significantly higher cancer detection rates for DBT+DM compared to DM. Four studies found no

significant differences in cancer detection rate, and one study did not report a test of statistical significance for the outcome.

Important Outcome: Cancer stage at diagnosis

None of the identified studies reported on the effects of DBT on cancer stage at diagnosis. Seven of the studies included in the systematic reviews reported on the percentage of detected cancers that were deemed invasive. For DBT+DM, 33% to 80% of the detected cancers were invasive compared to 50% to 74% for DM alone. Most of these studies reported similar or slightly higher rates of invasive disease among the cancers detected by DBT+DM compared to DM.

Important Outcome: Recall rate/false-positive test results

Among 11 studies included in the systematic reviews, nine found statistically significantly lower recall rates with DBT+DM compared to DM, and two found no difference. The reported recall rates ranged from 3.6% to 13.6% for DBT+DM and 4.2% to 16.2% for DM. The summary estimate of recall rates provided in the WA HTA report was 80–140 per 1,000 for DBT+DM and 100–160 per 1,000 for DM. The WA HTA report also found similar biopsy rates between the two groups (12–27 per 1,000 for DBT+DM vs. 14-22 per 1,000 for DM alone). In the WA HTA report, the estimate of the positive predictive value of biopsies indicated by DBT+DM was higher than that for biopsies indicated by DM alone (25–30% vs. 20–25%).

In the STORM study (Ciatto et al., 2013), the overall false-positive recall rate was 5.5%, with a significantly greater number of false-positive recalls attributable to DM (n=141) compared to DBT+DM (n=73). In the Oslo study (Skaane et al., 2013a), the overall false-positive recall rate for DBT+DM was lower than that of DM (5.3% vs. 6.1%, $p<0.01$).

Among the studies included in the systematic reviews, four studies found statistically significant increases in the positive predictive value of recall for DBT+DM compared to DM; three studies (two of which were conducted in Europe where overall recall rates are lower and the positive predictive value of recall is higher) found no significant differences in the positive predicative value of recall, and four studies either did not report on that outcome or did not report tests of statistical significance.

Key Question 2

Does the comparative effectiveness of DBT vary by the following characteristics:

a. Age
b. Race or ethnicity
c. Breast density

The STORM study (Ciatto et al., 2013) reported on cancer detection rate by age group and breast density. The incremental cancer detection rate of DBT+DM compared to DM was 1.7 per 1,000 among women under age 60 compared to 4.0 per 1,000 in women aged 60 years or older. The incremental cancer detection rate was similar among women with lower breast density (2.8 per 1,000) and higher breast density (2.5 per 1,000), although the authors cautioned that the small number of women with higher breast density limits the comparison.

In the retrospective study by Haas and colleagues (2013), DBT+DM was associated with statistically significant reductions in recall rates for women in all age groups with the exception of those women 70 years of age or older. The authors also reported statistically significant reductions in recall rates for women with any breast density classification other than predominantly fatty.

The systematic review by Melnikow and colleagues on screening for women with dense breasts (2016b) found that in three studies the cancer detection rate was superior with DBT+DM (5.4–6.9 per 1,000) compared to DM (4.0–5.2 per 1,000), with one study also demonstrating equivalent proportions of invasive cancers in both groups. The reported recall rates were also lower with DBT+DM (range 7% to 11%) compared to DM (9% to 17%).

Key Question 4

What are the harms of 3-D/2-D mammography compared to standard 2-D mammography alone?

Overdiagnosis occurs when noninvasive or indolent cancers that would not cause morbidity are identified during screening. Estimates of the percentage of breast cancers that represent overdiagnosis range from approximately 10% to 20% based on randomized controlled trials of mammography (Nelson et al., 2016a). None of the included studies of DBT specifically reported on overdiagnosis, although as noted above, the studies that reported on invasive cancers found similar proportions between DM and DBT+DM groups.

False-positive results have been associated with higher levels of breast-cancer worry and distress in three fair- to good-quality systematic reviews, but the effects of false-positive tests on screening reattendance, anxiety, and depression were mixed (Nelson et al., 2016). As noted above, the overall recall rate for DBT+DM is similar to, or slightly lower than, the recall rate for DM alone. Four studies found statistically significant improvements in the positive predictive value of initial recall with DBT+DM while two studies found no significant difference.

Estimates of the incidence of radiation-induced cancer death from mammography vary based on age and screening interval, but range from 2 per 100,000 to 11 per 100,000 (Nelson et al., 2016). DBT and DM require similar doses of radiation. When DBT and DM images are acquired separately, the dose of radiation is effectively doubled (Melnikow et al., 2016a). Technology that became available in 2013 allows reconstruction of two-dimensional images, thus limiting the radiation dose to that required for a single examination.

Key Question 5

If DBT is used as a primary screening modality, what is the optimal screening interval, and does that interval vary according to the characteristics listed in Key Question 2?

Because none of the studies followed participants beyond one year or through subsequent rounds of screening with DBT, the optimal screening interval with DBT cannot be established from the existing evidence.

Additional Studies

Sharpe et al., 2016

This is a single center retrospective cohort study of 85,852 examinations for asymptomatic women presenting for breast cancer screening between 2011 and 2014. In the overall cohort, there were 5,703 DBT+DM examinations (6.6%) and 80,149 DM examinations. Nearly all of the examinations (89%) were interpreted by 10 radiologists specializing in breast imaging; the remaining 11% were interpreted by lower volume general radiologists and these examinations were excluded from the recall rate analysis. There were baseline differences in patient characteristics between the DBT cohort and DM cohort. In the DBT cohort there were greater proportions of women with extremely dense breasts, family history of breast cancer, personal history of breast cancer, and a history of breast biopsy with benign findings compared to the DM cohort.

The cancer detection rate in the DM cohort was 3.5 per 1,000 (95% CI 3.1 to 3.9) compared to 5.4 per 1,000 (95% CI 3.7 to 7.8), resulting in an incremental cancer detection rate of 1.9 per 1,000 ($p<0.0018$). However, the invasive cancer detection rate was 2.46 per 1,000 in the DM cohort and 2.81 per 1,000 in the DBT+DM cohort, a difference that was not statistically significant ($p=0.61$). The detection rate for carcinoma in situ was 1.04 per 1,000 in the DM cohort and 2.63 per 1,000 in the DBT+DM cohort ($p<0.0006$).

The overall recall rate was statistically significantly lower in the DBT+DM cohort (6.10%) compared to the DM cohort (7.51%) ($p<0.0001$). Subgroups in which there were statistically significant differences in the recall rate (in favor of DBT) included women with heterogeneously or extremely dense breasts and women in their fifth and seventh decades. However, in a mixed-effects logistic regression model intended to account for other factors associated with differences in recall rates, the authors found that there was no association between the type of study and the risk of recall after the other factors were accounted for ($p=0.7459$).

Rose et al., 2014

This is a retrospective reading study in which seven radiologists from a single practice retrospectively interpreted the full-field DM images obtained from 10,878 DM+DBT examinations that had been prospectively interpreted by radiologists in a clinical setting. The retrospective readers interpreted the DM images at least 120 days after the examination was performed, and they were blinded to the original clinical interpretations and subsequent clinical course.

Of the 10,878 DBT+DM examinations that were prospectively interpreted, there were 588 recalls (5.4%) and 59 cancers detected (5.4 per 1,000, 81% invasive). In the retrospective reading of DM images alone, there would have been 888 recalls (8.2%) and 38 cancers detected (3.5 per 1,000, 76% invasive). For examinations that were indicated for recall only by retrospective review of the DM images, a third radiologist performed arbitration, and only 3 of these women were ultimately given a late recall; one of the late recalls resulted in a diagnosis of infiltrating lobular carcinoma and one resulted in a diagnosis of ductal carcinoma in situ. Of the 362 instances in which recall was indicated by DBT+DM but not by DM alone, there were 21 cancers detected, of which 19 were invasive. In the overall group, there was one case of breast cancer that was not screen detected over the course of one year of follow-up.

McDonald et al., 2016

This is a single center retrospective cohort study of 44,468 screening examination in 23,958 unique asymptomatic women between 2010 and 2014. In the first year (September 2010 to September 2011), 10,728 screening exams were performed using DM (denoted DM0 cohort). Between October 2011 and October 2014, 33,740 screening exams were performed using DBT (denoted DBT1, DBT2, or DBT3 cohorts based on the year the exam was performed). Information about the clinical course was taken from the medical record and the Pennsylvania State Cancer Registry (to assess the rate of interval cancers). There were no differences in the baseline patient characteristics between the DM0 and DBT3 cohorts.

The cancer detection rate was 4.6 per 1,000 in the DM0 cohort compared with 5.5 per 1,000 in the DBT1, 5.8 per 1,000 in the DBT2, and 6.1 per 1,000 in the DBT3 cohorts; none of the differences between the cancer detection rate in the DM0 cohort and each of the DBT cohorts were statistically significant. Similarly, there was no statistically significant difference in the rate of invasive cancer detection between the DM0 cohort and any of the DBT cohorts.

The recall rate in the DM0 cohort was 104 per 1,000 compared to 88 per 1,000, 90 per 1,000, and 92 per 1,000 in the DBT1, DBT2, and DBT 3 cohorts respectively. The difference in the recall rate was statistically significant between the DM0 cohort and each of the DBT cohorts. The overall biopsy rate was about 2% and did not differ between the cohorts. Notably, the recall rate for the most recent screening for women receiving serial rounds of DBT screening fell with each additional exam (78 per 1,000 in women who received two screenings and 59 per 1,000 in women who received three screenings).

The positive predictive value of recall (the number of cancers diagnosed per patients recalled to undergo biopsy, abbreviated PPV1) was 4.4% in the DM0 cohort, 6.2% in the DBT1 cohort, 6.5% in the DBT2 cohort, and 6.7% in the DBT3 cohort; the differences in PPV1 between the DM0 and DBT2 or DBT3 cohorts were statistically significant. The number of cancers per biopsy recommended (PPV2) and the number of cancers per biopsy performed (PPV3) were not statistically significantly different in comparing any of the cohorts. The interval cancer rate during the DM0 year was 0.7 per 1,000 compared to 0.5 per 1,000 in the DM1 year, a difference that was not statistically significant.

Lang et al., 2016

This is a prospective population-based single-arm screening cohort of asymptomatic Swedish women between the ages of 40 and 74 years. Among all women presenting to the screening program, 7,500 were randomly selected to undergo one-view DBT and two-view DM with independent, blinded double reading of the exams (double reading is a common practice in much of Europe). Six experienced readers interpreted all of the examinations; if either of the studies (DBT or DM) was interpreted as positive by one reader, that study was referred for arbitration by two other readers who made a final decision on recall. All of the follow-up evaluation for recalled patients was done at the same center. The average age of participating women was 56 years, and about 20% were undergoing their first screening examination; 34% had heterogeneously dense breasts and 8% had dense breasts.

Cancer was identified in 67 women in the DBT reading arm and 47 in the DM reading arms; 46 of the cancers were detected by both modalities, meaning that 21 cancers were detected only by DBT and one cancer was detected only by DM. The overall cancer detection rate was 8.9 per 1,000 (95% CI 6.9 to 11.3) for DBT and 6.3 per 1,000 (95% CI 4.6 to 8.3) for DM. The authors state that DBT offered a statistically significant increase in cancer detection of 43% over DM (95% CI 21% to 68%, p<0.0001). In contrast to most studies that involve sequential interpretation of DBT and DM images, in this study all of the cancers found in the DBT reading arm were identified by DBT images alone.

There were more recalls in the DBT reading arm (3.8%, 95% CI 3.3% to 4.2%) compared to the DM reading arm (2.6%, 95% CI 2.3% to 3.0%) The authors stated that DBT resulted in a statistically significant increase in the recall rate over DM of 43% (95% CI 26% to 62%, p<0.0001). The positive predictive value of recall was the same in both groups (24%). Of the 21 cancers detected in the DBT reading arm but not in the DM reading arm, 81% were invasive. There were no statistically significant differences in the cancer type, histologic grade, tumor size, or lymph node status between the cases detected only in the DBT reading arm and those detected in the DM reading arm, although the study was inadequately powered to detect such differences.

Conant et al., 2016

This is a retrospective cohort study involving 142,883 DM exams and 55,998 DBT exams performed at three centers in the Northeast U.S. between 2011 and 2014. The results from one of these centers were previously reported in part (Sharpe et al., 2016). At the second center, DBT+DM was offered based on availability and patient preference; at the third center, DBT+DM was used at the request of patients or providers or was targeted to women with dense breasts, baseline exams, or no previous imaging. Among the entire cohort, a smaller subset (25,268 DBT+DM exams and 113,061 DM exams) had at least 12 months of follow-up that allowed calculation of the overall cancer rate (derived from data from statewide cancer registries) and the sensitivity and specificity of the exams.

There were important baseline differences between the women in the DBT+DM cohort and the DM cohort with respect to age distribution (more younger women in the DBT cohort), race/ethnicity (more black women in the DBT cohort), breast density (more women with heterogeneously dense breasts in the DBT cohort), and first-time screening (more first-time screening exams in the DBT cohort). Additionally, nearly all of the women in the DM cohort came from two of the three study centers. The authors applied a prior logistic regression model meant to account for the differences in age, breast density, first-time screening, and research center.

Recall rates and biopsy rates were calculated for the overall cohort. The recall rate was 8.7% in the DBT+DM group compared to 10.4% in the DM group (odds ratio [OR] for recall in the adjusted analysis 0.68, 95% CI 0.65 to 0.71). The biopsy rate was 2% in the DBT+DM group compared to 1.8% in the DM group, but in the adjusted analysis the odds ratio for biopsy was lower in the DBT+DM group (OR 0.85, 95% CI 0.77 to 0.93). The reduction in recall for DBT+DM was greatest in women between age 40 and 49 and in women with dense breasts, but all subgroups showed a reduction in recall.

The cancer outcomes were calculated in the smaller cohort for individuals for whom at least 12 months of follow-up was available. The observed cancer rate was higher in the DBT+DM group (6.5 per 1,000)

than the DM group (4.9 per 1,000). The invasive cancer rate was 4.7 per 1,000 in the DBT+DM group and 3.7 per 1,000 in the DM group. The cancer detection rate was 5.9 per 1,000 in the DBT+DM group compared with 4.4 per 1,000 in the DM group (p=0.0026). The invasive cancer detection rate was 4.2 per 1,000 in the DBT+DM group and 3.3 per 1,000 in the DM group (p=0.0449). The false-negative rate was 0.60 per 1,000 in the DBT+DM group and 0.46 per 1,000 in the DM group (p=0.347). The positive predictive value of recall was 6.4% in the DBT+DM group and 4.1% in the DM group (p<0.0001). There was no difference in the sensitivity of the two exams (90.6% vs. 90.9%, p=1.00), but the specificity was higher for DBT+DM (91.3%) than for DM (89.7%) (p<0.0001).

Bernardi et al., 2016

This is a prospective double-reading study in which 9,672 asymptomatic women over the age of 49 in Northern Italy underwent both DM and DBT. There were two reading strategies. In the first strategy, two independent, experienced breast radiologists sequentially interpreted the separately acquired DM images and then the combined separately acquired DM+DBT images. In the second strategy, two independent, experienced breast radiologists sequentially interpreted synthetic DM images derived from DBT acquisition and then the combined synthetic DM+DBT images. A screening was deemed positive and recall initiated if either reader interpreted either one of the sequential images as positive. Screening detected 90 cancers in 85 women; 76 of the cancers detected were invasive. Of the 76 invasive cancers, 46 were detected by both standard DM alone and by the integrated screenings (DM+DBT and synthetic DM+DBT), and 28 were detected only by the integrated screening.

The cancer detection rate was 6.3 per 1,000 (95% CI 4.8 to 8.1) for DM alone compared with 8.5 per 1,000 (95% CI 6.7 to 10.5) for integrated DM+DBT and 8.8 per 1,000 (95% CI 7.0-10.8) for integrated synthetic DM+DBT. The improvements in the cancer detection rate for integrated strategies over DM alone were more pronounced in women under the age of 60 and women with heterogeneously or extremely dense breasts.

Compared to both of the integrated strategies, DM alone had a lower false-positive recall rate (3.42% vs. 3.97% for DM+DBT and 4.45% for synthetic DM+DBT.)The lower false-positive recall rate for DM alone was most pronounced among women with heterogeneously or extremely dense breasts.

The trial did not follow women in order to determine the rate of interval cancers that were not detected by screening.

Houssami & Turner, 2016

This is a rapid review and meta-analysis of cancer detection and recall rates for DBT in women with dense breasts. The authors divided the trials into prospective studies that compared screening detection in the same subjects between DM and DBT (Ciatto, 2013; Lang 2016; Bernardi, 2016; Tagliafico 2016), and retrospective studies that compared screening detection in different groups of subjects (Rose, 2013; McCarthy, 2014; Conant, 2016; Rafferty 2016). It should be noted that in one of the included trials (Tagliafico, 2016), the patients had been referred for adjunctive screening after a negative digital mammogram. In the meta-analysis of prospective studies, the incremental cancer detection rate was 3.9 additional cancers identified per 1,000 screens with DBT (95% CI 2.7 to 5.1). In the meta-analysis of the retrospective studies, the incremental cancer detection rate was 1.4 additional cancers identified per

1,000 screens with DBT (95% CI 0.9 to 2.0). Pooled estimates for the difference in recall rates could only be estimated from the retrospective trials; in that analysis, DBT resulted in 23.3 fewer recalls per 1,000 screens compared to DM (95% CI -29.9 to -16.8).

Summary of Additional Studies

Among the additional studies submitted during public comment or identified through searches:

- Five found increases in the cancer detection rate with DBT compared to DM (Sharpe, 2016; Rose, 2014; Lang, 2016; Conant, 2016; Bernardi, 2016), whereas one found no statistically significant difference (McDonald, 2016). However, in one of these trials (Sharpe, 2016), there was no statistically significant difference in the rate of invasive cancer detection, and the rate of recall did not differ between DBT and DM after accounting for other factors that influence recall in the mixed-effects logistic regression model.
- Four found decreases in the recall rate for DBT compared to DM (Sharpe, 2016; Rose, 2014; McDonald, 2016; Conant 2016), one study found an increase in the recall rate (Lang, 2016), and one found an increase in the false-positive recall rate (Bernardi, 2016).
- A rapid review and meta-analysis of trials with subgroups of women with dense breasts found an increase in the cancer detection rate and a decrease in the recall rate with DBT compared to DM (Houssami & Turner, 2016).

Economic Analyses

Kalra et al., 2016

This is a cost-effectiveness analysis of annual screening using DBT from the federal payer perspective over a lifetime horizon. The clinical inputs were derived from Friedewald et al.'s 2014 study that showed a 1.2 per 1,000 screenings increase in cancer detection rate and 16 per 1,000 screenings decrease in the recall rate with DBT over DM. Costs were determined from the 2015 Medicare reimbursement values and the costs, utilities, and disutility associated with invasive and noninvasive cancers were derived from published literature. There authors noted that there is no reference standard for the disutility associated with false-positive recall. The standard 3% annual discounting was applied. Across all age groups in the base-case scenario, DBT resulted in a net gain of 0.04 quality-adjusted life-years (QALYs) over DM; the cost per QALY gained over DM was estimated at $20,300. In the probabilistic sensitivity analysis (in which inputs are varied to create 10,000 simulations), DBT was cost-effective compared to DM at a willingness-to-pay threshold (WTP) of $100,000 per QALY in 63.2% of the scenarios. In the deterministic sensitivity analyses, DBT remains cost-effective (at a WTP of $100,000 per QALY) as long as the recall rate is reduced by at least 1 per 1,000 screens and the cost of DBT does not exceed $250 more than the cost of DM alone. One limitation of this analysis was "an inability to capture the downstream costs of work-up for false positive cases" and the authors noted that their model accounted only for radiologic biopsies, not costlier surgical biopsies. Additionally, the clinical inputs were derived from large academic practices with uncertain congruence to community practices.

Bonafede et al., 2015

This is an economic modeling study designed to estimate the cost impact of full conversion from DM to DM+DBT in a hypothetical commercial managed care plan. The critical input pertaining to the use of

follow-up diagnostic services for people undergoing DM+DBT is based on unpublished proprietary market research data furnished by Truven Health Analytics. Additionally, the model assumes that DM+DBT would shift the distribution of diagnosed breast cancers toward earlier stages, an assumption that is not clearly supported in the literature (cf. Lang, 2016). In the base-case analysis, the conversion from DM to DBT+DM would save $0.20 per member per month (PMPM) with a range (depending on the assumed rate of follow-up services for DBT+DM) of $0.37 PMPM to $0.03 PMPM.

Lee et al., 2014

This is a cost-effectiveness analysis comparing the biennial screening with DBT+DM to biennial screening with DM alone among women aged 50 to 74 with dense breasts from a federal payer perspective over a lifetime horizon. The operating characteristics of DBT+DM compared with DM for all women (not exclusive to women with dense breasts) were derived from the Oslo screening trial (Skaane, 2013); those operating characteristics were assumed to be the best-case scenario and the base-case scenario relied on more modest estimates of the performance of DBT+DM. The authors assumed an additional cost of $50 for DBT+DM over the cost of DM alone, but because of uncertainty in that estimate they used a wide range of costs in the sensitivity analysis. In the base case analysis, DBT+DM resulted in a gain of 0.007 QALYs over DM with an incremental cost per QALY gained of $53,893. In the sensitivity analysis, the best-case scenario for DBT performance, the incremental cost per QALY gained was $26,107 and $792,264 in the worst case scenario for DBT performance. Assuming a WTP of $100,000 per QALY, DBT+DM remains cost-effective up to an added cost of $87 over the cost of DM. A probabilistic sensitivity analysis was not performed.

Conclusions

The evidence for using DBT for breast cancer screening is limited to observational studies, most of which have methodological limitations and inadequate follow-up periods. Thus, the effects of DBT on all-cause mortality, breast cancer morbidity, and breast cancer stage at diagnosis are unknown. Two studies with adequate follow-up to ascertain interval cancer rates and thereby permit calculation of sensitivity and specificity reached differing conclusions; one of these trials showed increased sensitivity and similar specificity with DBT+DM, and the other study showed identical sensitivity and improved specificity with DBT+DM. Some of the conflicting results may be accounted for by differences in reading models and recall patterns between the United States and Europe. There is low-quality evidence with mixed results that DBT+DM improves cancer detection rates. There is low-quality evidence that DBT+DM reduces recall rates and increases the positive predictive value of recall compared to DM alone, particularly when limited only to studies that were performed in the United States. Among the U.S.-based studies, reduction in recall rate is the most consistent finding (see Table 4). However, with the exception of the population of women with dense breasts, there are no meta-analytic estimates available for any of the outcomes.

POLICY LANDSCAPE

Quality measures

No quality measures related to DBT specifically were identified when searching the National Quality Measures Clearinghouse.

Payer coverage policies

Coverage policies were assessed for Aetna, Cigna, Moda, and Regence. Aetna, Moda, and Regence do not cover DBT because of insufficient evidence for its effectiveness. Although Cigna did not cover DBT for routine breast cancer screening under its previous policy, Cigna revised its coverage policy on August 23, 2016, to permit DBT for routine breast cancer screening based on recent guidance from the National Comprehensive Cancer Network (Cigna, 2016).

The Washington Medicaid program covers DBT when performed with a screening mammography for patients aged 40 to 74 who are candidates for screening mammography. Prior authorization is required for mammograms with or without DBT for patients age 39 or younger.

For Medicare, no National Coverage Determinations or Local Coverage Determinations related to DBT were identified.

Professional society guidelines

The U.S. Preventive Services Task Force issued an I recommendation for DBT in 2016, concluding that there was insufficient evidence to assess the benefits and harms of DBT for screening (USPSTF, 2016), based on the AHRQ systematic review (Melnikow et al., 2016a). Furthermore, the USPSTF also issued an I recommendation for adjunctive or supplemental screening, including DBT, for women with dense breasts.

Similarly, the American Congress of Obstetricians and Gynecologists (ACOG), American Cancer Society (ACS), American College of Physicians (ACP), and American Academy of Family Physicians (AAFP) all considered DBT in their breast cancer screening guidelines, but concluded that current evidence is insufficient to assess its effectiveness (ACOG, 2011; Oeffinger et al., 2015; Wilt, Harris, & Qaseem, 2015; AAFP, 2016).

Although the American College of Radiology (ACR) did not address DBT in its previous 2010 breast cancer screening recommendations (Lee et al., 2010), it released a position statement in November 2014, which states that DBT is no longer investigational and has demonstrated improvement in outcomes compared to digital mammography. The ACR (n.d.) summarizes its own position statement as follows:

> "The ACR position on DBT is that it is no longer investigational. Tomosynthesis has been shown to improve key screening parameters compared to digital mammography." The College applauds the decision by the Centers for Medicare and Medicaid Services (CMS) to facilitate access to these exams by covering beneficiaries for tomosynthesis and urges private payers to do the same.

Under its recommendation for an annual screening mammogram for average risk women aged 40 and over, the National Comprehensive Cancer Network (NCCN) recently added, "Consider tomosynthesis" (p. 7, 2016).

REFERENCES

Evidence Sources

Bernardi, D., Macaskill, P., Pellegrini, M., Valentini, M., Fanto, C., Ostillio, L., ... Houssami, N. (2016). Breast cancer screening with tomosynthesis (3D mammography) with acquired or synthetic 2D mammography compared with 2D mammography alone (STORM-2): A population-based prospective study. *The Lancet Oncology*. DOI: 10.1016/s1470-2045(16)30101-2.

Bonafede, M. M., Kalra, V. B., Miller, J. D., & Fajardo, L. L. (2015). Value analysis of digital breast tomosynthesis for breast cancer screening in a commercially-insured US population. *ClinicoEconomics and Outcomes Research, 7*, 53-63. DOI: 10.2147/ceor.s76167.

Ciatto, S., Houssami, N., Bernardi, D., Caumo, F., Pellegrini, M., Brunelli, S., … Macaskill, P. (2013). Integration of 3D digital mammography with tomosynthesis for population breast-cancer screening (STORM): A prospective comparison study. *Lancet Oncology, 14*(7), 583-589. http://dx.doi.org/10.1016/S1470-2045(13)70134-7.

Conant, E. F., Beaber, E. F., Sprague, B. L., Herschorn, S. D., Weaver, D. L., Onega, T., ... Barlow, W. E. (2016). Breast cancer screening using tomosynthesis in combination with digital mammography compared to digital mammography alone: A cohort study within the PROSPR consortium. *Breast Cancer Research and Treatment, 156*(1), 109-116. DOI: 10.1007/s10549-016-3695-1.

Destounis, S., Arieno, A., & Morgan, R. (2014). Initial experience with combination digital breast tomosynthesis plus full field digital mammography or full field digital mammography alone in the screening environment. *Journal of Clinical Imaging Science, 4*(1), 1-6. DOI: 10.4103/2156-7514.127838.

Friedewald, S. M., Rafferty, E. A., Rose, S. L., Durand, M. A., Plecha, D. M., Greenberg, J. S., … Conant, E. F. (2014). Breast cancer screening using tomosynthesis in combination with digital mammography. *Journal of the American Medical Association, 311*(24), 2499-2507. DOI: 0.1001/jama.2014.6095.

Greenberg, J. S., Javitt, M. C., Katzen, J., Michael, S., & Holland, A. E. (2014). Clinical performance metrics of 3D digital breast tomosynthesis compared with 2D digital mammography for breast cancer screening in community practice. *Woman's Imaging, 203*(3), 1-7. DOI: 10.2214/AJR.14.12642.

Haas, B. M., Kalra, V., Geisel, J., Raghu, M., Durand, M., & Philpotts, L. E. (2013). Comparison of tomosynthesis plus digital mammography and digital mammography along for breast cancer screening. *Radiology, 269*(3), 694-700.

Houssami, N., & Turner, R. M. (2016). Rapid review: Estimates of incremental breast cancer detection from tomosynthesis (3D-mammography) screening in women with dense breasts. *Breast, 30*, 141-145. DOI: 10.1016/j.breast.2016.09.008.

Houssami, N., Macaskill, P., Bernardi, D., Caumo, F., Pellegrini, M., Brunelli, S., … Ciatto, S. (2014). Breast cancer screening using 2D-mammography or integrating digital breast tomosynthesis (3D-mammography) for single-reading or double-reading – Evidence to guide future screening strategies. *European Journal of Cancer, 50*(10), 1799-807.

Kalra, V. B., Wu, X., Haas, B. M., Forman, H. P., & Philpotts, L. E. (2016). Cost-effectiveness of tomosynthesis in annual screening mammography. *American Journal of Roentgenology*, 1-4. DOI: 10.2214/ajr.15.14487.

Lang, K., Andersson, I., Rosso, A., Tingberg, A., Timberg, P., & Zackrisson, S. (2016). Performance of one-view breast tomosynthesis as a stand-alone breast cancer screening modality: Results from the Malmo Breast Tomosynthesis Screening Trial, a population-based study. *European Radiology, 26*(1), 184-190. DOI: 10.1007/s00330-015-3803-3.

Lang, K., Andersson, I., Rosso, A., Tingberg, A., Timberg, P., & Sackrisson, S. (2015). Performance of one-view breast tomosynthesis as a stand-alone breast cancer screening modality: Results from the Malmo Breast Tomosynthesis Screening Trial, a population-based study. *European Radiology, 26*(1), 184-90. DOI: 10.1007/s00330-015-3803-3.

Lee, C. I., Cevik, M., Alagoz, O., Sprague, B. L., Tosteson, A. N., Miglioretti, D. L., ... Lehman, C. D. (2015). Comparative effectiveness of combined digital mammography and tomosynthesis screening for women with dense breasts. *Radiology, 274*(3), 772-780. DOI: 10.1148/radiol.14141237.

Lourenco, A. P., Barry-Brooks, M., Baird, G., Tuttle, A., & Mainiero, M. B. (2014). Changes in recall type and patient treatment following implementation of screening digital breast tomosynthesis. *Radiology,* 274(2), 337-42. DOI: http://dx.doi.org/10.1148/radiol.14140317.

McCarthy, A. M., Kontos, D., Synnestvedt, M., Tan, K. S., Heitjan, D. F., Schnall, M., & Conant, E. F. (2014). Screening outcomes following implementation of digital breast tomosynthesis in a general-population screening program. *Journal of the National Cancer Institute, 106*(11), 1-7. DOI: 10.1093/jnci/dju316.

McDonald, E. S., Oustimov, A., Weinstein, S. P., Synnestvedt, M. B., Schnall, M., & Conant, E. F. (2016). Effectiveness of digital breast tomosynthesis compared with digital mammography: Outcomes analysis from 3 years of breast cancer screening. *JAMA Oncology, 2*(6), 737-743. DOI: 10.1001/jamaoncol.2015.5536.

Melnikow, J., Fentron, J. J., Miglioretti, D., Whitlock, E. P., & Weyrich, M. S. (2016a). *Screening for breast cancer with digital breast tomosynthesis.* Rockville, MD: Agency for Healthcare Research and Quality. Retrieved from http://www.uspreventiveservicestaskforce.org/Home/GetFileByID/1925

Melnikow, J., Fentron, J. J., Miglioretti, D., Whitlock, E. P., Weyrich, M. S., Thompson, J. H., & Shah, K. (2016b). Supplemental screening for breast cancer in women with dense breasts: A systematic review for the U.S. Preventive Services Task Force. *Annals of Internal Medicine, 164*(4), 268-78. DOI: 10.7326/M15-1789.

Nelson, H. D., Pappas, M., Cantor, A., Griffin, H., Daeges, M., & Humphrey, L. (2016a). Harms of breast cancer screening: Systematic review to update the 2009 U.S. Preventive Services Task Force recommendation. *Annals of Internal Medicine, 164*(4), 256-267. DOI: 10.7326/M15-0970.

Rose, S. L., Tidwell, A. L., Ice, M. F., Nordmann, A. S., Sexton, R., Jr., & Song, R. (2014). A reader study comparing prospective tomosynthesis interpretations with retrospective readings of the corresponding FFDM examinations. *Academic Radiology, 21*(9), 1204-1210. DOI: 10.1016/j.acra.2014.04.008.

Rose, S. L., Tidwell, A. L., Bujnoch, L. J., Kushwaha, A. C., Nordmann, A. S., & Sexton, R. Jr. (2013). Implementation of breast tomosynthesis in a routine screening practice: An observational study. *Women's Imaging, 200*(6), 1401-1408. DOI: 10.2214/AJR.12.9672.

Sharpe, R. E., Jr., Venkataraman, S., Phillips, J., Dialani, V., Fein-Zachary, V. J., Prakash, S., ... Mehta, T. S. (2016). Increased cancer detection rate and variations in the recall rate resulting from implementation of 3D digital breast tomosynthesis into a population-based screening program. *Radiology, 278*(3), 698-706. DOI: 10.1148/radiol.2015142036.

Skaane, P., Bandos, A. I., Gullien, R., Eben, E. B., Ekseth, U., Haakenaasen, U., … Gur, D. (2013a). Comparison of digital mammography alone and digital mammography plus tomosynthesis in a population-based screening program. *Radiology, 267*(1), 47-56.

Skaane, P., Bandos, A. I., Gullien, R., Eben, E. B., Ekseth, U., Haakenaasen, U., … Hofvind, S. (2013b). Prospective trial comparing full-field digital mammography (FFDM) versus combined FFDM and tomosynthesis in a population-based screening programme using independent double reading with arbitration. *European Radiology, 23*(6), 2061-2071. DOI: 10.1007/s00330-013-2820-3.

Washington Health Technology Assessment Program (WA HTA). (2014). *Appropriate imaging for breast cancer screening in special populations.* Retrieved from http://www.hca.wa.gov/hta/documents/breast_imaging_draft_rpt_comments_response_121014.pdf

Other Citations

American Academy of Family Physicians. (2016, August). *Summary of recommendations for clinical preventive services.* Retrieved from http://www.aafp.org/dam/AAFP/documents/patient_care/clinical_recommendations/cps-recommendations.pdf.

American Cancer Society. (2016a). *Breast cancer: Breast cancer survival rates, by stage.* Retrieved from http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-survival-by-stage.

American Cancer Society. (2016b). *Breast cancer: Can breast cancer be found early?* Retrieved from http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-detection.

American Cancer Society. (2016c). *Breast cancer: What are the key statistics about breast cancer?* Retrieved from http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-key-statistics.

The American College of Obstetricians and Gynecologists. (2011). *Practice bulletin number 112: Breast Cancer Screening*. Retrieved from https://www.acog.org/-/media/Practice-Bulletins/Committee-on-Practice-Bulletins----Gynecology/Public/pb122.pdf?dmc=1&ts=20160809T1414023573.

American College of Radiology (ACR). (2014). *Position statements: ACR statement on breast tomosynthesis*. Retrieved from http://www.acr.org/About-Us/Media-Center/Position-Statements/Position-Statements-Folder/20141124-ACR-Statement-on-Breast-Tomosynthesis.

American College of Radiology (ACR). (n.d.). *Digital breast tomosynthesis.* Retrieved from http://www.acr.org/Advocacy/Economics-Health-Policy/Managed-Care-and-Private-Payer/Common-Coverage-Issues-with-Private-Payors/Digital-Breast-Tomosynthesis.

Centers for Disease Control and Prevention (CDC). (2016a). *Breast cancer statistics.* Retrieved from https://www.cdc.gov/cancer/breast/statistics/index.htm.

Centers for Disease Control and Prevention (CDC). (2016b). *Breast cancer: What are the risk factors for breast cancer?* Retrieved from http://www.cdc.gov/cancer/breast/basic_info/risk_factors.htm.

Centers for Disease Control and Prevention (CDC). (2012). *Vital signs: Breast cancer*. Retrieved from http://www.cdc.gov/vitalsigns/breastcancer/.

Cigna. (2016*). Cigna revises policy, will cover 3D mammography for breast cancer screening*. Retrieved from http://www.cigna.com/newsroom/news-releases/2016/cigna-revises-policy-will-cover-3d-mammography-for-breast-cancer-screening.

Helvie, M.A. (2010). Digital mammography imaging: Breast tomosynthesis and advanced applications. *Radiologic clinics of North America*, *48*(5), 917-926. DOI: 10.1016/j.rcl.2010.06.009. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3118307/

Lee, C. H., Dershaw, D. D., Kopans, D., Evans, P., Monsees, B., Monticciolo, D., ... Burhenne, L. W. (2010). Breast cancer screening with imaging: Recommendations from the Society of Breast Imaging and the ACR on the use of mammography, breast MRI, breast ultrasound, and other technologies for the detection of clinically occult breast cancer. *Journal of the American College of Radiology, 7*(1), 18-27. DOI:10.1016/j.jacr.2009.09.022.

National Cancer Institute at the National Institutes of Health. (2016*). Breast cancer prevention (PDQ®)—Health professional version*. Retrieved from http://www.cancer.gov/types/breast/hp/breast-prevention-pdq

National Comprehensive Cancer Network (NCCN). (2016). *Breast cancer screening and diagnosis*. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/breast-screening.pdf

Nelson, H. D., Fu, R., Cantor, A., Pappas, M., Daeges, M., & Humphrey, L. (2016b). Effectiveness of breast cancer screening: A systematic review and meta-analysis to update the 2009 U.S. Preventive Services Task Force recommendation. *Annals of Internal Medicine, 164*(4), 244-255. DOI: 10.7326/M15-0969.

Oeffinger, K. C., Fontham, E. T., Etzioni, R., Herzig, A., Michaelson, J. S., Shih, Y. C., ... Wender, R. (2015). Breast cancer screening for women at average risk: 2015 guideline update from the American Cancer Society. *JAMA, 314*(15), 1599-1614. DOI:10.1001/jama.2015.12783.

United States Food and Drug Administration (U.S. FDA). (2015). *Frequently asked questions about DBZT and MQSA training requirements*. Retrieved from http://www.fda.gov/Radiation-EmittingProducts/MammographyQualityStandardsActandProgram/FacilityCertificationandInspection/ucm447869.htm.

U.S. Preventive Services Task Force (USPSTF). (2016). *Final recommendation statement: Breast cancer screening*. Retrieved from http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/breast-cancer-screening.

Wilt, T. J., Harris, R. P., & Qaseem, A. (2015). Screening for cancer: Advice for high-value care from the American College of Physicians. *Annals of Internal Medicine, 162*(10), 718-725. DOI: 10.7326/M14-2326.

Suggested citation: Obley, A., Mosbaek, C., Hackett, R., & Livingston, C. (2016). *Coverage guidance: Digital breast tomosynthesis (3D mammography) for breast cancer screening in average risk women*. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University.

APPENDIX A. GRADE INFORMED FRAMEWORK – ELEMENT DESCRIPTIONS

Element	Description
Balance of benefits and harms	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. An estimate that is not statistically significant or has a confidence interval crossing a predetermined clinical decision threshold will be downgraded.
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 in the absence of likely cost offsets—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.
Other considerations	Other considerations include issues about the implementation and operationalization of the technology or intervention in health systems and practices within Oregon.

Strong recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the balance of benefits and harms, resource allocation, values and preferences, and other factors.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the balance of benefits and harms, resource allocation, values and preferences, and other factors.

Weak recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the balance of benefits and harms, resource allocation, values and preferences, and other factors, but further research or additional information could lead to a different conclusion.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the balance of benefits and harms, cost and resource allocation, and values and preferences, but further research or additional information could lead to a different conclusion.

Confidence in estimate rating across studies for the intervention/outcome[4]

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 estimate of effect: 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

[4] Includes risk of bias, precision, directness, consistency, and publication bias.

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 estimate of effect 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 estimate of effect: 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. GRADE EVIDENCE PROFILE

Quality Assessment (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
All-cause mortality							
0	NA	NA	NA	NA	NA	NA	NA
Breast cancer morbidity							
0	NA	NA	NA	NA	NA	NA	NA
Test performance characteristics/Cancer detection rate (CDR)							
17 (for CDR) 2 (for sensitivity and specificity)	Mix of observational studies	Low to moderate	Not serious	None	Not serious	Sparse data for sensitivity and specificity	Low for CDR ●●○○ Very low for sensitivity and specificity ●○○○
Stage at diagnosis							
0	NA	NA	NA	NA	NA	NA	NA
Recall rate/False-positive rate							
16	Mix of observational studies	Low to moderate	Not serious	None	Not serious	NA	Low ●●○○

APPENDIX C. METHODS

Scope Statement

Populations

Women between the ages of 40 and 74 years referred for breast cancer screening

Population scoping notes: *Excludes women with a personal history of breast cancer, clinically significant BRCA gene mutations, Li-Fraumeni syndrome, Cowden syndrome, hereditary diffuse gastric cancer or other familial breast cancer syndromes, high-risk lesions (ductal or lobular carcinoma in situ, atypical ductal or lobular hyperplasia), or previous large doses of chest radiation therapy (≥ 20 Gy) before age 30 years.*

Interventions

DBT (3-D mammography) in conjunction with standard 2-D digital mammography

Intervention exclusions: *None*

Comparators

Standard 2-D mammography with or without computer-aided diagnosis

Considered but not selected: No screening, MRI, ultrasound

Outcomes

Critical: All-cause mortality, breast cancer morbidity

Important: Test performance characteristics, cancer stage at diagnosis, recall rate/false-positive test results

Considered but not selected for the GRADE table: Cancer-specific mortality, radiation exposure, PPV for recalls, PPV for biopsies

Key Questions

KQ1: What is the comparative effectiveness of digital breast DBT as a primary screening modality in women referred for breast cancer screening?

KQ2: Does the comparative effectiveness of DBT vary by the following characteristics:

a. Age
b. Race or ethnicity
c. Breast density

KQ3: In a screening population, how do the test characteristics of 3-D/2-D mammography compare to those of standard 2-D mammography?

KQ4: What are the harms of 3-D/2-D mammography compared to standard 2-D mammography alone?

KQ5: If DBT is used as a primary screening modality, what is the optimal screening interval, and does that interval vary according to the characteristics listed in Key Question 2?

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using the terms Digital Breast Tomosynthesis and 3-dimensional (3-D) mammography. Searches of core sources were limited to citations published in the past five years.

The core sources searched included:

- Agency for Healthcare Research and Quality (AHRQ)
- Blue Cross/Blue Shield Health Technology Assessment (HTA) program
- BMJ Clinical Evidence
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Interscience)
- Hayes, Inc.
- Institute for Clinical and Economic Review (ICER)
- Medicaid Evidence-based Decisions Project (MED)
- National Institute for Health and Care Excellence (NICE)
- Tufts Cost-effectiveness Analysis Registry
- Veterans Administration Evidence-based Synthesis Program (ESP)
- Washington State Health Technology Assessment Program

A MEDLINE® search was conducted to identify systematic reviews, meta-analyses, and technology assessments published in the past five years. A MEDLINE® search was then conducted to identify randomized control trials and cohort studies that would have been included in the identified systematic reviews except for being published after the search dates of the systematic reviews.

Searches for clinical practice guidelines were limited to those published since 2011. A search for relevant clinical practice guidelines was also conducted, using the following sources:

- Australian Government National Health and Medical Research Council (NHMRC)
- Centers for Disease Control and Prevention (CDC) – Community Preventive Services
- Choosing Wisely
- Institute for Clinical Systems Improvement (ICSI)
- National Guidelines Clearinghouse
- New Zealand Guidelines Group
- NICE
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Preventive Services Task Force (USPSTF)
- Veterans Administration/Department of Defense (VA/DOD)

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessments, or clinical practice guidelines.

APPENDIX D. APPLICABLE CODES

CODES	DESCRIPTION
ICD-10 Diagnosis Codes	
Z12.31	Encounter for screening mammogram for malignant neoplasm of breast
CPT Codes	
77051	Computer-aided detection with further physician review for interpretation; diagnostic mammography
77052	Computer-aided detection with further physician review for interpretation; screening mammography
77055	Mammography; unilateral
77056	Mammography; bilateral
77057	Screening mammography; bilateral
77061	Digital breast tomosynthesis; unilateral
77062	Digital breast tomosynthesis; bilateral
77063	Screening digital breast tomosynthesis; bilateral (in addition to primary screening mammography procedure)
HCPCS Level II Codes	
G0202	Screening mammography; producing direct digital image, bilateral, all views
G0204	Diagnostic mammography, producing direct digital image, bilateral, all views
G0206	Diagnostic mammography, producing direct digital image, unilateral, all views
G0279	Diagnostic digital breast tomosynthesis; unilateral or bilateral

Note: Inclusion on this list does not guarantee coverage.

Digital Breast Tomosynthesis (3D Mammography)
for Breast Cancer Screening in Average Risk Women

Question: Should digital breast tomosynthesis (DBT) be included on the preventive services line for average risk women?

Question source: HTAS

Issue: HTAS has developed a coverage guidance addressing digital breast tomosynthesis. Based on the evidence, HTAS has issued a weak recommendation that digital breast tomosynthesis should not be covered for breast cancer screening in average risk women.

Rationale for decision: There is no data, utilizing DBT for screening in average risk women, related to the critical outcomes of all-cause mortality and breast cancer morbidity. However, recognizing that data on long-term effects take time to accrue, HTAS also included important outcomes related to the operating characteristics of DBT.

Based on observational studies performed in the US, it is likely that DBT decreases recall rates as compared with digital mammography (DM) alone. We have low confidence that DBT improves cancer detection rates, due to low quality evidence with mixed results. We are also not confident that any improvement in cancer detection rates with DBT, if clearly demonstrated, would result in cancers being detected at earlier stages, leading to earlier intervention that improves clinical outcomes. Adding DBT to standard DM adds cost, and we are not confident that DBT is cost-effective, based on current analysis. Additionally, randomized controlled trials are currently underway that should help with greater understanding of the risks and benefits of DBT+DM, including the critical issue of whether DBT improves clinical outcomes. The recommendation against coverage is a weak recommendation because further evidence could change the recommendation.

This HTAS coverage guidance only addresses the use of DBT in population screening of average risk women and does not address the use of DBT as a diagnostic test. In addition, breast cancer screening for above average risk women will be addressed in a subsequent HTAS coverage guidance.

Current Prioritized List status:

CPT code	**Code Description**	**Placement**
77063	Screening digital breast tomosynthesis; bilateral (in addition to primary screening mammography procedure)	Services Recommended for Non-Coverage

HERC staff recommendation:

1) Make no change in the placement of digital breast tomosynthesis
    a. Keep CPT 77063 on the Services Recommended for Non-Coverage Table

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Table of Contents

Discussion Table

IDs/#s	Summary of Issue	Subcommittee response
A1, A3, C1, E1	Additional evidence and guidelines to be considered	The newly submitted studies and guidelines have been incorporated into the coverage guidance.
A2, B1, D1	Concerns pertaining to the selection of all-cause and cancer-specific morbidity and mortality as critical outcomes	HERC strives to select outcomes that are most appropriate to the intervention under consideration and reflect patient-important results that would influence decisions regarding coverage. Large-scale population screening trials frequently examine and report on the effects of screening on all-cause and cancer-specific mortality. Rigorously designed screening trials are necessary to avoid common and well-described pitfalls of observational screening trials, including lead-time bias and length-time bias, and to account for possible overdiagnosis and other harms of screening. However, recognizing that data on long-term effects take time to accrue, HERC also included outcomes related to the operating characteristics of DBT.

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Commenters

Identification	Stakeholder
A	Legacy Health *[Submitted September 30, 2016]*
B	Diane Coady, R.T.R.M. *[Submitted October 12, 2016]*
C	John Griffith *[Submitted October 14, 2016]*
D	Sheven Thorson *[Submitted October 14, 2016]*
E	Kari A. Thomas, MD *[Submitted October 14, 2016]*

Public Comments

ID/#	Comment	Disposition
A1	Legacy is concerned that the HERC draft recommendation regarding digital breast tomosynthesis (DBT) has overlooked recent data that directly addresses the specific concerns of the HERC regarding DBT efficacy, as well as pertinent cost analysis. Due to the omission of these relevant studies from the HERC's literature review, we feel the panel's recommendations are not fair to the evidence, which is a disservice to our patients, and for all women in Oregon. For nearly four years, Legacy physicians and patients have experienced the advantage of increased cancer detection rates and decreased recall rates afforded by the early adoptions of DBT technology in our breast centers. In our experience, the additional cancers detected by DBT are primarily invasive; introduction of DBT into our practice has not significantly increased in situ cancer detection. The HERC review appears to have only considered studies that were included in previous systematic reviews by the USPSTF and the Washington HTA, which are incomplete and outdated. As a result, while the HERC review included eleven studies, it does not include the six important clinical publications listed below. Collectively, these publications report the findings of more than 350,000 mammograms: 1. Conant 2016	*Thank you for your comments. The listed studies, along with other recent observational studies, have been added as evidence sources in the coverage guidance.*

ID/#	Comment	Disposition
	2. Bernardi 2016 3. McDonald 2016 4. Sharpe 2015 5. Lang 2015 6. Rose 2014 In particular, Conant 2016 is important because it comprises results of almost 200,000 exams in the United States. We respectfully request that the panel consider the results of these studies and amend the recommendation to cover DBT accordingly. Each of the six studies listed above showed a statistically significant increase in cancer detection. Taken together with the five additional studies noted by the HERC, the statistically significant increase in cancer detection from DBT is made clear by the results of nearly 900,000 mammograms. In contrast, the four studies noted by the HERC which showed no statistically significant increase in cancer detection only report the results of just over 88,000 mammograms. The evidence is clear and consistent: tomosynthesis has a higher cancer detection rate than digital mammography alone. The HERC review states that there is "very low confidence" in recall rate estimates. Recall rates are lower in Europe than in the US, as noted by the HERC. If only US-based data are considered, there are eleven studies showing a statistically significant reduction in recall rate with DBT, and NONE that find no change. The evidence is clear and consistent: tomosynthesis has a lower recall rate than digital mammography alone in the US.	

HERC Coverage Guidance – Digital Breast Tomosynthesis (3D Mammography) for Breast Cancer Screening in Average Risk Women
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ID/#	Comment	Disposition
A2	Regarding outcomes, to require evidence of reduced all-cause mortality and/or breast cancer morbidity is unnecessary for an improved mammogram. This type of evidence was not required when digital mammography became an acceptable alternative to film mammography and should NOT be required for DBT to become an acceptable alternative to digital mammography. As detailed above by more recent literature, DBT improves the benefits provided by digital mammography alone by having a higher cancer detection rate, while reducing the harms of false positive recalls.	*Thank you for your comments. While one might consider DBT merely to be an "improved mammogram," its use as a proposed primary screening modality should be subject to the normal evidentiary standards for screening tests. Large-scale population screening trials frequently examine and report on the effects of screening on all-cause and cancer-specific mortality. Rigorously designed screening trials are necessary to avoid common and well-described pitfalls of observational screening or diagnostic accuracy studies including lead-time bias, length-time bias, and to account for possible overdiagnosis and other harms of screening. However, recognizing that data on long-term effects take time to accrue, HERC also included outcomes related to the operating characteristics of DBT.*
A3	Regarding cost, 2016 comparative effectiveness data that is not included in the HERC literature review shows the benefits outweigh the DBT cost, and debunks the hypothesis that the cost of DBT would negatively impact the system at a population level.	*Thank you for your comments. Additional economic studies have been included as evidence sources in the coverage guidance—see C1 below.*
A4	Also of note, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for 2016 issued a Category 1 recommendation for DBT, meaning this applies to all	*Thank you for your comments. We have added the NCCN guidelines to the coverage guidance.*

ID/#	Comment	Disposition
	populations for annual screening mammography. This is the highest recommendation NCCN awards. The NCCN is a leader in defining and advancing high-quality, high-value oncology care.	
A5	Time and again, Legacy patients have benefitted from DBT—many invasive breast cancers would not have been detected otherwise, and fewer patients have been unnecessarily recalled for additional imaging. If the aim of the HERC is to improve patient care, population health, and the cost-effectiveness of health care in Oregon and across the country, approval for coverage of DBT is critical.	*Thank you for your comments.*
B1	I believe the HERC is inadvertently holding DBT to an unfair standard to provide coverage. Digital mammography never had to prove such a strict standard of endpoints when it surpassed film mammography, and DBT is so much more superior to 2D in the published studies than 2D was to film, it is astounding to those of us in the breast imaging community that you would recommend non-coverage in your draft. I have found a similarity to CT colonography to help explain my point. Regarding the use of all-cause mortality as a "critical outcome" for diseases where screening is recommended, the need to demonstrate that a test with superior accuracy also improves all-cause mortality is unnecessarily restrictive and results in an unnecessary delay in access to improved screening. Using all-cause mortality as a critical outcome for an improved breast cancer screening test is also inconsistent with the approach taken for colon cancer. New colon cancer screening tests, such as CT colonography and fecal immunochemical testing, are considered as acceptable screening strategies based on performance characteristic studies alone. The latest USPSTF review did not identify any studies which evaluate the all-cause mortality of these tests, yet the USPSTF found sufficient evidence that are acceptable alternatives to traditional colonoscopy. Since you rely heavily on the USPSTF in your draft review, I thought this was relevant. This same approach should be taken for mammography. The evidence clearly demonstrates that breast tomosynthesis detects more cancers (increased sensitivity) with fewer false positives (increased specificity) when compared to traditional 2D mammography. If 2D mammography is	*Thank you for your comments. See A2 above. Additionally, it is common for HERC to consider patient-important outcomes and other factors when examining the evidence for any intervention, including screening interventions. HERC would most likely apply the same standards to CT colonography were it being considered for a coverage guidance.*

<table>
<tr><th>ID/#</th><th>Comment</th><th>Disposition</th></tr>
<tr><td></td><td>acceptable, breast tomosynthesis should also be an option for women who undergo breast cancer screening.</td><td></td></tr>
<tr><td>C1</td><td>I urge you to reverse your position of non-payment for breast tomosynthesis based on sound medical evidence that it is cost-effective.

Three economic analyses of breast tomosynthesis have been published in peer-reviewed journals. These studies are summarized below.

<table>
<tr><th>Study</th><th>Analysis Type</th><th>Patient population</th><th>Incremental QALY*</th><th>Incremental costs</th><th>ICER**</th><th>Conclusion</th></tr>
<tr><td>Lee 2014</td><td>Cost-effectiveness</td><td>Routine biennial screening of women with dense breasts age 50-74</td><td>0.007</td><td>$349</td><td>$53,893</td><td>“Biennial combined digital mammography and tomosynthesis screening for US women aged 50–74 years with dense breasts is likely to be cost-effective if priced appropriately (up to $226 for combined examinations vs. $139 for digital</td></tr>
</table></td><td>Thank you for your comments. The listed studies have been added as evidence sources in the coverage guidance.</td></tr>
</table>

ID/#	Comment							Disposition
							mammography alone) and if reported interpretive performance metrics of improved specificity with tomosynthesis are met in routine practice."	
	Bonafede 2015	Budget Impact	Routine screening of women age 40-74	N/A	$28.53 saved per screening exam	N/A	"The results of this study demonstrate clinical and economic favourability of DBT for breast cancer screening among commercially insured US women. Wider adoption of DBT mam-mography presents an opportunity to deliver value-	

ID/#	Comment							Disposition
							based care in the US health care system."	
	Kalra 2016	Cost-effectiveness	Routine annual screening of women age 40-79	0.04	$812	$20,230	"Addition of annual screening tomosynthesis to 2D mammography beginning at the age of 40 years was cost-effective compared with 2D mammography alone in our analysis. Three times greater net monetary benefits were found in women 40–49 years old compared with those 50–59 years old."	

** QALY: Quality-Adjusted Life Years; ** ICER: Incremental Cost-Effectiveness Ratio.*

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ID/#	Comment	Disposition
D1	With regard to your approach of evaluating outcomes data including recall rate, biopsy rate, and cancer detection, I believe there are some fundamental issues considering this is a screening technology not a pharmaceutical drug or other therapy. I do not disagree with the approach, in general, but I do disagree with the position that this is the type of outcome data the HERC should look for when evaluating a screening or diagnostic technology. The National Institute of Health articulates this position very clearly in its publication "Fundamental Concepts for Health Technology Assessments": ***"Beyond technical performance of screening and diagnostic tests, their effect on health outcomes or health-related quality of life is often less immediate or direct than for other types of technologies****. The impacts of most preventive, therapeutic, and rehabilitative technologies on health outcomes can be assessed as direct cause-and-effect relationships between interventions and outcomes.* ***However, the relationship between the use of screening and diagnostic tests and health outcomes is typically indirect, given intervening decisions or other steps between the test and health outcomes.*** *Even highly accurate test results may be ignored or improperly interpreted by clinicians. Therapeutic decisions that are based on test results can have differential effects on patient outcomes. Also, the impact of those therapeutic decisions may be subject to other factors, such as patient adherence to a drug regimen..."* It is a fact that better detection of invasive cancer improves outcomes—a study with DBT is not necessary to prove this point. Furthermore, it is unlikely such a study will ever be conducted because it would be considered unethical and inhumane to allow breast cancer to progress to more advanced stages and eventual death in the control group, not to mention that it would take 10-20 years to compile meaningful data. DBT improves cancer detection and PPV for biopsy and reduces recall rates compared to digital mammography alone. To boil this down, if you believe in mammography as a screening tool (which I assume you do since your policy supports it today) then there should be no question for you to add coverage of DBT, considering that all exams include a 2D, and it is therefore impossible for DBT to ever perform	*Thank you for your comments. See A2 above. Additionally, we would interpret the points made by the NIH regarding the indirectness of test operating characteristics as ultimately favoring stronger study designs meant to demonstrate that in real-world practice a screening test actually leads to patient-important outcomes. Furthermore, the improvement in invasive cancer detection is not uniform across the studies included in the coverage guidance and the effects on recall are similarly mixed. Lastly, several randomized controlled trials of DBT as a screening modality are currently underway.*

ID/#	Comment	Disposition
	worse than 2D alone. Beyond logic, the published studies show that DBT enhances mammography screening compared to 2D alone. On the other hand, if you don't believe in mammography as a screening tool, then it will be very difficult for you to ever find a reason to cover DBT, and logically you should actually remove coverage of 2D because it wouldn't even pass the criteria bar you have set for DBT in this analysis. In my opinion, the HERC is treating the DBT analysis like it would a drug or therapeutic treatment. Instead, it needs to step back and look at DBT for what it is: a screening technology that enhances 2D mammography, reduces recalls, improves PPV for biopsy and finds cancer earlier, end of story. Thus its impacts long-term outcomes and economics for the state in a positive way. I am asking that you not simply fall in line with the outdated USPSTF review or the outdated WA TEC assessment like your draft guidance appears to do. Instead, evaluate the published US studies and if you determine that DBT enhances performance over 2D alone, add it to coverage.	
E1	The HERC draft recommendation does not accurately characterize the overall quantity, quality, and consistency of the evidence. **Quantity of Evidence** There are 11 major clinical trials (7 US, 4 European) which compare breast cancer screening with digital breast tomosynthesis (DBT) to screening with digital mammography (DM) alone. The HERC draft review only included 6 of these studies. The following studies, which evaluate a total of 347,579 exams, should be included in the review: Rose 2014, Lang 2015, Sharpe 2015, McDonald 2016, Conant 2016. The draft review also incorrectly evaluates five "secondary" manuscripts as if they are independent of their "primary" manuscript, which also appears in the review. For example, the review appears to characterize the Greenberg 2014, Haas 2013, and McCarthy 2014 manuscripts as unique studies. In reality, these manuscripts report single center data from the Friedewald 2014 multicenter study, which is already included in the review. While these "secondary" studies do	*Thank you for your comments. The listed studies, along with other recent observational studies and a new rapid review and meta-analysis, have been added as evidence sources in the coverage guidance. We have also delineated which studies were performed in the United States and which were performed in other countries.* *In GRADE methodology, observational trials begin as low-quality evidence. None of the other factors applied to observational trials would be sufficient to upgrade the evidence (large magnitude of effect, plausible confounding in the*

ID/#	Comment	Disposition
	include some endpoints not presented in primary manuscript, the cancer detection and recall results are duplicative of those included in the Friedewald 2014 manuscript. A complete list of the 11 studies which contain a significant number of unique exams is provided in the table below. **Quality of Evidence** While all 11 studies evaluating DBT are observational and may be considered lower quality evidence than randomized controlled trials, the panel should separately consider studies which evaluate DBT and DM exams which were contemporaneously acquired in the same population. Observational studies are subject to selection bias due to potential population differences in the experimental and control groups. Such selection bias is not possible in five of the DBT screening trials (Ciatto 2013, Skaane 2013, Rose 2014, Lång 2015, Bernardi 2016) because these studies evaluated DBT and DM in the same patient population, and thus patients served as their own controls. Therefore, these studies should be considered as a higher level of evidence than studies which evaluate two different population groups. **Consistency of evidence** While each of the 11 DBT screening studies has a lower quality observational design, the panel should consider the volume and consistency of the evidence when evaluating multiple studies. In total, the 11 DBT screening studies evaluated more than 850,000 examinations and consistently demonstrated that the use of DBT increases the rate of cancer detection while reducing the recall/false positive rate. <u>Breast Cancer Detection</u> Eight of the 11 DBT screening trials reported that DBT detects breast cancer at a significantly greater ($p<0.001$) rate than DM alone. These studies evaluated a total of 787,556 exams and reported a 27-55% relative increase in the rate of cancer detection. All five of the higher quality	*direction of effectiveness, or dose-response relationship)* .

ID/#	Comment	Disposition
	studies in which patients served as their own controls demonstrated a statistically significant increase in cancer detection. Three smaller studies evaluating a total of 71,014 exams found no statistically significant increase in cancer detection. While a formal meta-analysis would be difficult due to differences in study design and patient population, there is a clear trend toward increased cancer detection when all 11 studies are considered together. In total, the 11 studies evaluated 330,522 DBT exams which detected 1,727 total cancers (5.23 cancers/1000 exams) and 576,021 DM exams which detected 2,340 cancers (4.06 cancers/1000 exams). Using this approach, the three studies which did not show a statistically significant increase in cancer detection did demonstrate an overall trend towards increased cancer detection. In these studies, there were 229 total cancers detected in 47,185 total DM+DBT exams (4.9 cancers/1000 exams) and 92 total cancers detected in 23,829 total DM alone exams (3.9 cancers/1000 exams). <u>Recall/False Positive Rates</u> Nine of the 11 DBT trials reported that DBT resulted in a statistically significant decrease in recall/false positive rate. These studies evaluated a total of 840,398 exams and reported a 13-63% relative decrease in the recall/false positive rate. Both studies which demonstrated an increase in recall rate with DBT were conducted in Europe, and one of these studies included a significant bias because DBT information was used during arbitration for all cases. As double reading is common in Europe (unlike the US), and recall rates are significantly lower in Europe than the US, it is most appropriate to consider US studies to understand the impact of DBT on recall in the US. All 7 studies conducted in the US demonstrated a statistically significant reduction in recall rate.	

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References Provided by Commenters

ID/#	References
A	Bernardi, D., Macaskill, P., Pellegrini, M., Valentini, M., Fanto, C., Ostillio, L., ... Houssami, N. (2016). Breast cancer screening with tomosynthesis (3D mammography) with acquired or synthetic 2D mammography compared with 2D mammography alone (STORM-2): A population-based prospective study. *The Lancet Oncology, 17*(8), 1105-1113. DOI: 10.1016/s1470-2045(16)30101-2. Conant, E. F., Beaber, E. F., Sprague, B. L., Herschorn, S. D., Weaver, D. L., Onega, T., ... Barlow, W. E. (2016). Breast cancer screening using tomosynthesis in combination with digital mammography compared to digital mammography alone: A cohort study within the PROSPR consortium. *Breast Cancer Research and Treatment, 156*(1), 109-116. DOI: 10.1007/s10549-016-3695-1. Lang, K., Andersson, I., Rosso, A., Tingberg, A., Timberg, P., & Zackrisson, S. (2016). Performance of one-view breast tomosynthesis as a stand-alone breast cancer screening modality: Results from the Malmo Breast Tomosynthesis Screening Trial, a population-based study. *European Radiology, 26*(1), 184-190. DOI: 10.1007/s00330-015-3803-3. McDonald, E. S., Oustimov, A., Weinstein, S. P., Synnestvedt, M. B., Schnall, M., & Conant, E. F. (2016). Effectiveness of digital breast tomosynthesis compared with digital mammography: Outcomes analysis from 3 years of breast cancer screening. *JAMA Oncology, 2*(6), 737-743. DOI: 10.1001/jamaoncol.2015.5536. Rose, S. L., Tidwell, A. L., Ice, M. F., Nordmann, A. S., Sexton, R., Jr., & Song, R. (2014). A reader study comparing prospective tomosynthesis interpretations with retrospective readings of the corresponding FFDM examinations. *Academic Radiology, 21*(9), 1204-1210. DOI: 10.1016/j.acra.2014.04.008. Sharpe, R. E., Jr., Venkataraman, S., Phillips, J., Dialani, V., Fein-Zachary, V. J., Prakash, S., ... Mehta, T. S. (2016). Increased cancer detection rate and variations in the recall rate resulting from implementation of 3D digital breast tomosynthesis into a population-based dcreening program. *Radiology, 278*(3), 698-706. DOI: 10.1148/radiol.2015142036.
C	Bonafede, M. M., Kalra, V. B., Miller, J. D., & Fajardo, L. L. (2015). Value analysis of digital breast tomosynthesis for breast cancer screening in a commercially-insured US population. *ClinicoEconomics and Outcomes Research, 7*, 53-63. DOI: 10.2147/ceor.s76167. Kalra, V. B., Wu, X., Haas, B. M., Forman, H. P., & Philpotts, L. E. (2016). Cost-Effectiveness of Tomosynthesis in Annual Screening Mammography. *American Journal of Roentgenology, 1-4*. DOI: 10.2214/ajr.15.14487.

ID/#	References
	Lee, C. I., Cevik, M., Alagoz, O., Sprague, B. L., Tosteson, A. N., Miglioretti, D. L., ... Lehman, C. D. (2015). Comparative effectiveness of combined digital mammography and tomosynthesis screening for women with dense breasts. *Radiology, 274*(3), 772-780. DOI: 10.1148/radiol.14141237.
E	Conant, E. F., Beaber, E. F., Sprague, B. L., Herschorn, S. D., Weaver, D. L., Onega, T., ... Barlow, W. E. (2016). Breast cancer screening using tomosynthesis in combination with digital mammography compared to digital mammography alone: A cohort study within the PROSPR consortium. *Breast Cancer Research and Treatment, 156*(1), 109-116. DOI: 10.1007/s10549-016-3695-1. Lang, K., Andersson, I., Rosso, A., Tingberg, A., Timberg, P., & Zackrisson, S. (2016). Performance of one-view breast tomosynthesis as a stand-alone breast cancer screening modality: Results from the Malmo Breast Tomosynthesis Screening Trial, a population-based study. *European Radiology, 26*(1), 184-190. DOI: 10.1007/s00330-015-3803-3. McDonald, E. S., Oustimov, A., Weinstein, S. P., Synnestvedt, M. B., Schnall, M., & Conant, E. F. (2016). Effectiveness of digital breast tomosynthesis compared with digital mammography: Outcomes analysis from 3 years of breast cancer screening. *JAMA Oncology, 2*(6), 737-743. DOI: 10.1001/jamaoncol.2015.5536. Rose, S. L., Tidwell, A. L., Ice, M. F., Nordmann, A. S., Sexton, R., Jr., & Song, R. (2014). A reader study comparing prospective tomosynthesis interpretations with retrospective readings of the corresponding FFDM examinations. *Academic Radiology, 21*(9), 1204-1210. DOI: 10.1016/j.acra.2014.04.008. Sharpe, R. E., Jr., Venkataraman, S., Phillips, J., Dialani, V., Fein-Zachary, V. J., Prakash, S., ... Mehta, T. S. (2016). Increased cancer detection rate and variations in the recall rate resulting from implementation of 3D digital breast tomosynthesis into a population-based dcreening program. *Radiology, 278*(3), 698-706. DOI: 10.1148/radiol.2015142036.

Section 7.0

New Discussion Items

Fecal Microbiota Transplant

Question: Should fecal transplant be added to the Prioritized List as a treatment for recurrent C. difficile infection?

Question source: coverage guidance process

Issue: Fecal microbiota transplant (FMT) is a rapidly evolving area for treatment of C. difficile colitis (C difficile infection or CDI). This procedure involves transplanting donor feces into the intestinal tract of a patient with CDI, either via a nasogastric tube, endoscope, enema or colonoscope. There is also ongoing research into using a capsule form of administration. Generally, this procedure is reserved for patients who have been treated with several courses of antibiotics with high activity against CDI and who still have significant symptoms. FMT is rapidly becoming a standard therapy for treatment of recurrent CDI.

C Difficile colitis can cause severe diarrhea, fever and abdominal pain. It can lead to pseudomembranous colitis, toxic megacolon, perforation of the colon, sepsis, and death. This infection generally occurs after a patient has been treated for an infection with antibiotics or has been hospitalized.

FMT is also being investigated as a treatment for inflammatory bowel disease (IBD). At this time, the FDA requires an investigational license for this use of fecal transplant.

Fecal transplant was reviewed as a new CPT code in 2012 and found to be experimental at that time. Since that review, several new studies have been published. Recently, Washington HTA conducted a systematic review of the topic.

Current code placements:
ICD-10 A04.7 (Enterocolitis due to Clostridium difficile) is on line 150 ENTERIC INFECTIONS AND OTHER BACTERIAL FOOD POISONING

CPT 44705 (Preparation of fecal microbiota for instillation, including assessment of donor specimen) is currently SNRC

HCPCS G0455 (Preparation with instillation of fecal microbiota by any method, including assessment of donor specimen) is currently SNRC

Evidence

1) **Washington HTA 2016 (document not included due to length, please view online: http://www.hca.wa.gov/assets/program/fmt-final-report-20161005.pdf)**
    a. N=27 (7 randomized trials, 5 cohort studies, and 15 case series)
    b. After a single treatment, significantly more FMT patients (previously treated 1-3 times with antibiotics) achieved cure through 2.5 months than those in the vancomycin group (pooled RD 45% (95% CI 25%, 64%))
    c. Pooled results suggest no difference in mortality attributed to CDI within 2.5 months of treatment (pooled RD 0% (95% CI -9%, 8%)) in FMT vs vancomycin groups
    d. The pooled effect estimate suggests no difference between FMT and vancomycin groups in all-cause mortality through 2.5 months (RD -4% (95% CI -14%, 7%))
    e. Adverse events: No serious adverse events were attributed to the FMT or colonoscopy procedures. *Non-serious adverse events:* A number of procedure-related adverse events were collected through one week of the procedure; other than chills, which occurred in slightly fewer donor FMT than autologous FMT patients (data NR, p=0.053), there was no difference between groups
    f. Cost utility analysis: FMT via colonoscopy was found to be dominant[124] or more cost effective compared to vancomycin in all four studies of patients with recurrent CDI. Conclusions were similar when comparing FMT to metronidazole or fidaxomicin. For the initial CDI occurrence, one study found that FMT via colonoscopy was dominant over vancomycin alone. In general, sensitivity analyses supported the conclusion that FMT was more cost-effective than antibiotic treatment for first or recurrent CDI.
    g. Summary of results:
        i. For patients with recurrent CDI and randomized to FMT or vancomycin, there was low quality evidence for the following outcomes as evaluated through 2.5 months. Cure was achieved by 45% (95% CI 25% to 64%) more patients following a single FMT (+ bowel lavage) procedure compared with vancomycin (± bowel lavage) therapy. To that end, the need for additional FMT procedure(s) for treatment of recurrent CDI (after the initial allocated treatment) was greater in the FMT group than in the vancomycin group. The incidence of CDI-related as well as all-cause mortality were similar across both groups. One trial additionally provided low quality evidence of no difference between groups in all-cause mortality through eight months.
        ii. For patients with recurrent CDI and randomized to FMT (donor feces) or placebo (autologous feces), moderate quality evidence from one small trial supports the following conclusions. Through two months, cure was 28% more likely following FMT than placebo (95% CI 6%, 51%); similarly, 33% fewer FMT patients underwent an additional FMT procedure due to recurrent CDI (after the initial allocated treatment) compared with the placebo group. Finally, no patients died in either group from any cause through six months.
        iii. For IBD: For patients with UC, moderate quality evidence suggests that clinical remission with an endoscopic response was slightly more common with FMT versus placebo through 1.75 months, however, both trials were terminated early due to lower remission rates than anticipated. No difference was found between groups in the percentage of patients who achieved clinical response through 1.75 months (low quality evidence) or in clinical remission through three months (moderate quality evidence); the need for additional procedures was also similar between groups through three months (low quality evidence).

iv. Based on results from the five included cost utility analyses, there was a suggestion that FMT was more cost-effective than antibiotic treatment for first or recurrent CDI.

2) **AHRQ 2016 (document not included due to length, please view online: https://effectivehealthcare.ahrq.gov/ehc/products/604/2208/c-difficile-update-report-160502.pdf**
   a. N=26 studies (3 RCTs, 23 observational studies)
   b. Based on a qualitative analysis of the unpooled data, low-strength evidence showed that FMT resolves diarrhea and prevents relapse in people with recurrent CDI.
   c. Data insufficient for patients with refractory CDI
3) **NICE 2014 (document not included due to length, please view online: https://www.nice.org.uk/guidance/ipg485/resources/faecal-microbiota-transplant-for-recurrent-clostridium-difficile-infection-1899869993554885)**
   a. Current evidence on the efficacy and safety of fecal microbiota transplant for recurrent *Clostridium difficile* infection is adequate to support the use of this procedure
   b. This procedure should only be considered for patients with recurrent *C. difficile* infections that have failed to respond to antibiotics and other treatments.

Expert guidelines

1) **American College of Gastroenterology 2013**
   a. If there is a third recurrence after a pulsed vancomycin regimen, fecal microbiota transplant (FMT) should be considered. (Conditional recommendation, moderate-quality evidence)
2) **European Society of Clinical Microbiology and Infectious Diseases, 2014**
   a. FMT in combination with oral antibiotic treatment is strongly recommended for multiple, recurrent C. difficile infections unresponsive to antibiotic treatment.

Other policies:
All major insurers cover FMT for treatment of recurring or refractory CDI after two or more courses of appropriate antibiotics.

HERC staff summary:
Trusted sources (AHRQ, Washington HTA, NICE) have all found that FMT is more effective than antibiotic therapy for resolution of recurrent CDI based on low quality evidence. FMT is cost effective compared to antibiotic therapy. There are few adverse events related to this therapy. Expert groups recommend its use for treatment of recurrent CDI.

There is minimal evidence to support the use of FMT for treatment of IBD.

HERC staff recommendations:

1) Add coverage for fecal microbiota transplant for treatment of recurrent C Difficile infection
    a. Add CPT 44705 (Preparation of fecal microbiota for instillation, including assessment of donor specimen) to line 150 ENTERIC INFECTIONS AND OTHER BACTERIAL FOOD POISONING and remove from the Services Recommended for Non-Coverage Table
    b. Add HCPCS G0455 (Preparation with instillation of fecal microbiota by any method, including assessment of donor specimen) to line 150 ENTERIC INFECTIONS AND OTHER BACTERIAL FOOD POISONING and remove from the Services Recommended for Non-Coverage Table
    c. Would not be available to treat IBD as these diagnoses are not included on line 150
2) Consider adding the following new guideline note to line 150
    a. FMT may become first line therapy for CDI and therefore a guideline may need to be addressed in the future.

GUIDELINE XXX FECAL MICROBIOTA TRANSPLANT

Line 150

Fecal microbiota transplant (FMT; CPT 44705, HCPCS G0455) is included on this line for treatment of recurrent C difficile infection only.

Gallstones and Cholecystitis

Questions:
1) What conditions should be included on the upper gallstone line for treatment with cholecystectomy?
2) Should a guideline be added to clarify when cholecystitis is present?

Question source: OHP medical directors; HERC staff; Dr. Jack Hartley, community surgeon

Issue: Gallstones (cholelithiasis) are present in 7% of the population, and more common in women and with increasing age. Gallstones can be asymptomatic, or can cause acute abdominal pain, called biliary colic. Cholecystitis occurs when the gallbladder becomes inflamed, and results in more prolonged pain and generally fever. The gallbladder is tender to palpation. Other signs of gallbladder inflammation included a thickened gallbladder wall on ultrasound, positive HIDA scan, etc. Approximately 20% of patients with gallstones will become symptomatic within 15 years of follow-up, 1-2% will develop other complications and the majority of these complications will occur in patients with biliary colic. Acalculous cholecystitis is clinically identical to acute cholecystitis but is not associated with gallstones and usually occurs in critically ill patients. It accounts for approximately 10% of cases of acute cholecystitis and is associated with high morbidity and mortality rates.

Gallstones are on both a covered and an uncovered line on the Prioritized List, with placement determined by the presence or absence of cholecystitis or obstruction. If cholecystitis is present, the diagnosis is included on line 59 COMPLICATED STONES OF THE GALLBLADDER AND BILE DUCTS; CHOLECYSTITIS; if not, the diagnosis is included on line 645 GALLSTONES WITHOUT CHOLECYSTITIS. There is no guideline to define when cholecystitis is present. Significantly, general surgeons feel that symptomatic gallstones (i.e. with biliary colic but without cholecystitis) should be included on the covered line. Whether to include symptomatic gallstones without cholecystitis on the upper line has been discussed twice in the past 10 years, in 2009 and 2012. There continues to be tension between community surgeons and the CCOs regarding whether painful gallstones/biliary colic should be an indication for cholecystectomy.

The decision to date by the HSC/HERC has been to only cover gallstones in the presence of cholecystitis or other complication. Given the overlap of symptoms between biliary colic and cholecystitis, the medical directors feel that there is a need for a definition of when cholecystitis is present. In 2004, Alison Little proposed a guideline to define cholecystitis; the decision was made to not adopt this guideline unless there was additional input from medical directors or surgeons that a guideline was needed:

> CHOLECYSTECTOMY GUIDELINE
> Presence of RUQ abdominal pain
> AND
> Presence of gallstones or evidence of gall bladder wall thickening on ultrasound
> OR
> Non-visualization of the gall bladder on oral cholecystegram or HIDA scan
> OR
> Gallbladder ejection fraction of < 35%

Currently cholecystectomy is covered for gallstones in the presence of acute or chronic cholecystitis, gallbladder or liver cancer, congenital anomalies of the GI system and of the gallbladder, paralytic ileus of the intestine, and for other “specified diseases of the gallbladder.”

Other issues related to the gallbladder

ICD-10 K82.8 (Other specified diseases of gallbladder) is present on both gallbladder lines without any guideline indicating when this condition is intended to be included for treatment on the upper line. K82.8 includes several subdiagnoses: adhesions/atrophy/cyst/hypertrophy/ulcer of cystic duct or gallbladder, biliary dyskinesia, gallbladder mass, intramural calcification of the gallbladder and porcelain gallbladder.

Porcelain gallbladder is an uncommon manifestation of chronic cholecystitis, characterized by intramural calcification of the gallbladder wall. Patients with a porcelain gallbladder are often asymptomatic, but are at increased risk for the development of gallbladder carcinoma, which has a poor prognosis. Intramural calcification can be present to a lesser degree as well, and simply diagnosed as calcification of the gallbladder.

Biliary dyskinesia is a symptomatic functional disorder of the gallbladder whose precise etiology is unknown. In order to diagnose biliary dyskinesia, the patient should have right upper quadrant pains similar to biliary colic but have a normal ultrasound examination of the gallbladder. Biliary dyskinesia is diagnosed by HIDA scan, with an abnormal scan showing <35% ejection fraction. Cholecystectomy is the only known effective treatment for the diagnosis of biliary dyskinesia. The likelihood of symptom relief at one year after cholecystectomy is variable and highly dependent on patient selection but ranges from 50-70%.

Current Prioritized List status:

47544 (Removal of calculi/debris from biliary duct(s) and/or gallbladder, percutaneous, including destruction of calculi by any method (eg, mechanical, electrohydraulic, lithotripsy) when performed, imaging guidance (eg, fluoroscopy), and all associated radiological supervision and interpretation) is on lines 59,105,298

47562 (Laparoscopy, surgical; cholecystectomy) is on lines 59,198,311,320,439

47563 (Laparoscopy, surgical; cholecystectomy with cholangiography) is on lines 59,198,439

47564 (Laparoscopy, surgical; cholecystectomy with exploration of common duct) is on lines 59,298,439,645

47600-47620 (Cholecystectomy) are on lines 59,105,298,320,439,645

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
198 HEREDITARY ANEMIAS, HEMOGLOBINOPATHIES, AND DISORDERS OF THE SPLEEN
298 ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER
311 PARALYTIC ILEUS
320 CANCER OF LIVER
439 CANCER OF GALLBLADDER AND OTHER BILIARY
645 GALLSTONES WITHOUT CHOLECYSTITIS

ICD-10 K85.1 (Biliary acute pancreatitis) is on line 199 ACUTE PANCREATITIS. This ICD-10 code represents gallstone pancreatitis.

HSC/HERC history

1) Coverage of painful gallstones without cholecystitis was discussed in August of 2009

From VBBS minutes:

Cholelithiasis with cholecystitis

Smits reviewed a document outlining problems the health plans are having with list placement and line names for lines dealing with cholelithiasis. The HSC has always intended that asymptomatic gallstones should be placed on an uncovered line. The discussion first centered around whether symptomatic gallstones should be covered. Saha wondered if there could be an obstructing stone without some type of cholecystitis. Gubler stated that pain without other signs of cholecystitis is relatively rare. Pathology usually comes back chronic inflammation. Surgeons generally do not remove gallstones which are only found incidentally based on Interqual guidelines. Kirk responded that Interqual guidelines used to be "biliary colic and evidence of inflammation," but the new version is "more than one incidence of biliary colic." He did not feel that renaming the upper line "Clinically significant" would work. Saha stated that the HSC needs to make clear that we won't pay for this unless there is active infection or active pain due to their gallstones. The discussion then centered around whether pain should be an indication. Kirk asked about the statistics for complications in people with colic. Gubler stated that the majority will develop cholecystitis without treatment. If there is no colic, only 10% will develop complications. Saha proposed attaching a guideline or SOI to the cholecystitis lines. Such a guideline would state "Asymptomatic cholelithiasis with or without pathologic diagnosis of cholelithiasis is not covered." However, Gubler argued that surgeons don't want to watch diabetics with stones, even if they don't have pain or complications, due to higher complication rates when untreated. Dodson felt that the HSC should just leave it the way it is, that the HSC can't mandate that a provider take a good history. The decision was to make no changes to the current lines other than the simple code changes proposed in the summary document.

2) Coverage of cholecystectomy was reviewed in the 2012 ICD-10 General surgery review. From the August, 2012 VBBS minutes:

The data on symptomatic and asymptomatic gallstones was reviewed. There was a discussion about the evidence and expected recurrence, as well as the significant risk of performing surgeries in patients with incidentally found gallstones who present with abdominal pain. Given the data demonstrating safety associated with conservative (non-surgical) management, and the large proportion of individuals who will not go on to develop further episodes, the decision was made to continue the current line structure.

Evidence—delayed cholecystectomy for uncomplicated biliary colic

1) **Gurusamy 2013**, **(Article not included in packet due to length; please view online:** http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007196.pub3/epdf) Cochrane review of early vs delayed cholecystectomy for uncomplicated biliary colic
    a. N=1 trial (75 participants—35 early laparoscopic cholecystectomy, 40 delayed cholecystectomy)
        i. Mean waiting period for delayed group 4.2 months
        ii. Trial deemed at high risk of bias
    b. Mortality: 0/35 (early) vs 1/40 (delayed, 2.5%) (P > 0.9999).
    c. There were no serious adverse events related to the surgery in either group.
    d. Complications in delayed group: pancreatitis (n = 1), empyema of the gallbladder (n = 1), gallbladder perforation (n = 1), acute cholecystitis (n = 2), cholangitis (n = 2), obstructive jaundice (n =2), and recurrent biliary colic (requiring hospital visits) (n = 5). In total, 14 participants required hospital admissions for the above symptoms. The proportion of people who developed serious adverse events was 0/28 (0%) in the early group, which was significantly lower than in the delayed laparoscopic cholecystectomy group 9/40 (22.5%) (P = 0.0082). This trial did not report quality of life or return to work.
    e. There was no significant difference in the proportion of people who required conversion to open cholecystectomy in the early group 0/28 (0%) compared with the delayed group (6/35 or 17.1%) (P = 0.0743). There was a statistically significant shorter hospital stay in the early group than in the delayed group (MD -1.25 days, 95% CI -2.05 to -0.45). There was a statistically significant shorter operating time in the early group than the delayed group (MD -14.80 minutes, 95% CI -18.02 to -11.58).
    f. **Authors' conclusions:** Based on evidence from only one high-bias risk trial, it appears that early laparoscopic cholecystectomy (less than 24 hours after diagnosis of biliary colic) decreases the morbidity during the waiting period for elective laparoscopic cholecystectomy (mean waiting time 4.2 months), the hospital stay, and operating time. Further randomised clinical trials are necessary to confirm or refute these findings
2) **Palmar 2015,** prognostic normogram for management of symptomatic cholelithiasis in older patients
    a. Medicare claims data study of outcomes for patients aged 65 and older who did not receive cholecystectomy within 2.5 months of first episode of biliary colic. Evaluated risk for cholecystectomy or hospitalization at 2 yrs
    b. N=92,436 patients with biliary colic/dyskinesia (65.3%), acute cholecystitis (26.6%), choledocholithiasis (5.7%), or gallstone pancreatitis (2.4%).
    c. The 2-year emergent gallstone-related hospitalization rate was 11.1%, with associated in-hospital morbidity and mortality rates of 56.5% and 6.5%. Factors associated with gallstone-related acute hospitalization included male sex, increased age, fewer comorbid conditions, complicated biliary disease on initial presentation, and initial presentation to the emergency department.
    d. Biliary colic was the lowest risk of the diagnoses evaluated
    e. **Conclusions:** Surgeons can use this prognostic nomogram to accurately provide patients with their 2-year risk of developing gallstone-related complications, allowing patients and physicians to make informed decisions in the context of their symptom severity and its impact on their quality of life.

Expert guidelines

1) **Society of American Gastrointestinal and Endoscopic Surgeons 2010**, guidelines for laparoscopic cholecystectomy (document is here: https://www.sages.org/publications/guidelines/guidelines-for-the-clinical-application-of-laparoscopic-biliary-tract-surgery/#)
    a. Asymptomatic gallstones are generally not an indication for laparoscopic cholecystectomy.
    b. Indications for laparoscopic cholecystectomy include but are not limited to symptomatic cholelithiasis, biliary dyskinesia, acute cholecystitis, and complications related to common bile duct stones including pancreatitis with few relative or absolute contraindications (Level II, Grade A).
    c. Patients with symptoms of biliary obstruction without evidence of gallstones, but with abnormal gallbladder emptying [biliary dyskinesia] may benefit from laparoscopic cholecystectomy. (Level II, Grade B).
    d. Patients with suspected gallbladder calcifications should be carefully studied, with open cholecystectomy recommended for those with selective mucosal calcifications. (Level III, Grade B).
    e. Laparoscopic cholecystectomy should be considered for larger, especially single, [gallbladder] polyps or those with associated symptoms, with watchful waiting for small (< 5mm) asymptomatic polyps. (Level II, Grade B).
    f. Laparoscopic cholecystectomy is considered curative for cancers confined to the gallbladder mucosa (T1a). (Level II, Grade B).
    g. Cancers which are more locally advanced or those with nodal involvement should be referred to specialty centers for consideration of more extensive resection or re-resection. (Level II, Grade B).
2) **Yokoe 2013**, updated Tokyo guidelines for diagnosis of cholecystitis (document found here: http://download.springer.com/static/pdf/155/art%253A10.1007%252Fs00534-012-0568-9.pdf?originUrl=http%3A%2F%2Flink.springer.com%2Farticle%2F10.1007%2Fs00534-012-0568-9&token2=exp=1483488131~acl=%2Fstatic%2Fpdf%2F155%2Fart%25253A10.1007%25252Fs00534-012-0568-9.pdf%3ForiginUrl%3Dhttp%253A%252F%252Flink.springer.com%252Farticle%252F10.1007%252Fs00534-012-0568-9*~hmac=1ff4bb2466d6dd834a6bab214aba8f398e5384223d6062550833914f49d52bd1
    a. TG13 diagnostic criteria for acute cholecystitis
        A. Local signs of inflammation etc.
            (1) Murphy's sign, (2) RUQ mass/pain/tenderness
        B. Systemic signs of inflammation etc.
            (1) Fever, (2) elevated CRP, (3) elevated WBC count
        C. Imaging findings
            Imaging findings characteristic of acute cholecystitis
        Suspected diagnosis: One item in A + one item in B
        Definite diagnosis: One item in A + one item in B + C

Other policies:
All other major insurers and CMS cover cholecystectomy for biliary colic, as well as cholecystitis or other complications.

Expert input

Dr. Jack Hartley

The requirement for fever or abnormal laboratory values excludes a significant number of patients with cholecystitis. 20% of patients with cholecystitis will have the disease confirmed by HIDA scanning. (Ann.Emer Med.1996 Sept 28(3):267-72). The presence of normal laboratory values does not exclude cholecystitis.

The indications for surgery should include the diagnosis of biliary colic or symptomatic cholelithiaisis. Biliary colic is the indication for a significant number of cholecystectomies. Biliary colic is defined as the presence of typical right upper quadrant pain and the presence of gall stones on imaging without signs of inflammation as indicated by abnormal lab values and imaging.

2010 SAGES guidelines recommend surgery for symptomatic cholelithiasis.

I would agree with your suggested compromise of covering recurrent biliary colic. In one report, over half of patients with complicated biliary tract disease (acute cholecystitis, pancreatitis, CBD stones) had biliary colic by history. Operating in the presence of more advanced disease is more prone to complications or the need to convert to an open procedure. At this time, laparoscopic cholecystectomy is widely practiced and the individual surgeons should have enough experience with the technique to avoid a significant incidence of complications.

Dr. Hartley provided several references to support his argument that cholecystectomy should be covered for biliary colic:

1) Duncan 2012: evidence based review of gallstone disease (document here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3496004/pdf/nihms408614.pdf)
    a. Biliary colic and acute cholecystitis are best treated with early laparoscopic cholecystectomy.
        i. Based on evidence of increased complication rate, increased ER visits, and reduced rates of conversion to open cholecystectomy.
        ii. Major evidence source cited is the Cochrane review included above
2) Besselink 2009: retrospective cohort study of incidence of biliary colic prior to complicated gallstone disease
    a. N=175 patients with complicated gallstone disease [pancreatitis (n=53), symptomatic common bile duct (CBD) stones (n=64), and acute cholecystitis (n=58)] and 175 patients with symptomatic uncomplicated gallstones were interviewed at admission.
    b. 57% (100 of 175) of patients with complicated disease (95% confidence interval=50–65%) experienced “warning” episodes of biliary colic (pancreatitis 58%, CBD stones 67%, cholecystitis 45%) vs 96% (164 of 175) in uncomplicated disease.
    c. Conclusions: Half of patients with biliary pancreatitis experience “warning” episodes of biliary colic, similar to other gallstone complications. In symptomatic patients, complications are often not prevented because of significant delays in diagnosis and treatment.

OHP CCO input:

Tracy Muday, MD, medical director Western Oregon Advanced Health

Utilization: 98 requests for cholecystectomy in the past year, with 18 of these denied.
In general, I think I am in favor of adding biliary colic to the covered line and calling it something like "symptomatic gallbladder diseases." I think the absolute number of surgeries would be small. Our plan is around 20,000 members, so this would be 5 extra surgeries per year per 10,000 members. At 1 million on the plan, does that come out to about 500 extra gallbladders a year statewide? Fewer if some plans are more permissive than we are.

Jim Calvert, MD, medical directorCascade Comprehensive

I think if a person has persistent pain from their gallbladder, or consistently recurrent pain, then it is medically appropriate to have a cholecystectomy. Usually this is associated with obvious stones and often an abnormal nuclear med gallbladder function test (HIDA) but not always – sometimes it is just a clinically apparent issue but the tests are equivocal or negative. So in those situations I would favor surgery. It would have to be recurrent- I would not get surgery with just one or two gallbladder attacks but not cholecystitis.

I don't really know if 2 of 3 signs is ok- I still think clinical judgment would play a role- so probably if 2 of 3 are present and the surgeon feels surgery is appropriate that is good enough.

Mark Maddox, MD, MVIPA

The decision that needs to be made is about coverage for symptomatic disease; is there a desire to cover biliary colic or not. The objective portion of the examination would be key and UM would be difficult given the subjective nature. I would not base indication on a specific number of "events", in other words, either cover it or don't cover it. I don't know of any risks of biliary colic.

For cholecystitis, either 2/3 or 3/3 is reasonable.

HERC staff summary:
There has been a longstanding debate at the HSC/HERC regarding coverage of cholelithiasis with biliary colic or other pain related to gallstones. The evidence and expert guidelines all agree that complications from gallstones, including cholecystitis, pancreatitis, gallbladder obstruction, etc. should be treated with cholecystectomy; all also agree that asymptomatic gallstones should not be treated surgically. The major area of disagreement is biliary colic. Expert guidelines recommend cholecystectomy for biliary colic. Poor quality studies show a significant complication rate for painful but otherwise uncomplicated cholelithiasis that is not treated by cholecystectomy, with approximately 20% of patients developing significant complications including death within 2 years. Evidence shows that many patients with complications of gallstones initially had biliary colic; however, it is unclear how many patients with biliary colic will go on to have complications. Previous discussions of coverage of cholecystectomy for biliary colic determined that the risks of surgery outweighed the risks of complications with conservative (non-operative) treatment, particularly for first time presentations.

In a similar situation, the HSC/HERC has consistently determined that painful but otherwise uncomplicated inguinal hernias should not have surgical treatment covered. Painful but otherwise uncomplicated inguinal hernias are recommended for surgical treatment by expert guidelines, and have a reported complication rate (obstruction, gangrene) of 1-2% per year.

Additionally, there is confusion regarding when cholecystitis is present, with expert guidelines including criteria for “definite” and “probable” cholecystitis. Using the expert criteria for definite cholecystitis would exclude some patients with disease. Using probable criteria would allow treatment of painful gallstones depending on how imaging is interpreted. HERC staff recommend adoption of a new guideline clearly indicating the intent of the HERC for defining when cholecystitis is present.

HERC staff recommendations:

1) Housekeeping
    a. Add cholecystectomy to line 199 ACUTE PANCREATITIS for pairing with gallstone pancreatitis (ICD10 K85.1)
        i. 47562 (Laparoscopy, surgical; cholecystectomy)
        ii. 47563 (Laparoscopy, surgical; cholecystectomy with cholangiography)
        iii. 47564 (Laparoscopy, surgical; cholecystectomy with exploration of common duct)
        iv. 47600-47620 (Cholecystectomy)
    b. Remove 47562 (Laparoscopy, surgical; cholecystectomy) from line 311 PARALYTIC ILEUS
        i. No appropriate diagnosis for pairing on this line
2) Do not include first episode of biliary colic as a condition present on the upper gallstone line
    a. Consider including recurrent biliary colic on the upper line (see below)
3) Adopt the guideline shown below for lines 59 and 645
    a. In #2, "or" correlates with suspected diagnosis (yellow highlight)
        i. Alternative: "and" instead of "or" would correlate with a definite diagnosis of cholecystitis in the Tokyo 2013 guidelines
    b. The wording in blue highlight would allow recurrent biliary colic to be included on the upper gallstone line
        i. Alterative: specify that biliary colic (initial or recurrent) without other complications is included on line 645

GUIDELINE NOTE XXX, CHOLECYSTITIS

Lines 59, 645

Cholecystitis is defined as

1) The presence of right upper quadrant abdominal pain, mass, tenderness or a positive Murphy's sign, AND
2) Evidence of inflammation (e.g. fever, elevated white blood cell count, elevated C reactive protein), OR
3) Ultrasound findings characteristic of acute cholecystitis or non-visualization of the gall bladder on oral cholecystegram or HIDA scan, or gallbladder ejection fraction of < 35%

Recurrent biliary colic (i.e. more than one episode of abdominal pain with gallstones seen on imaging) without evidence of cholecystitis or other complications is included on line 59.

ICD-10 K82.8 (Other specified diseases of gallbladder) is included on line 59 when the patient has

1) Porcelain gallbladder, or
2) Gallbladder dyskinesia with a gallbladder ejection fraction <35%.

Otherwise, K82.8 is included on line 645.

Ann Surg. Author manuscript; available in PMC 2016 Jun 1.
Published in final edited form as:
Ann Surg. 2015 Jun; 261(6): 1184–1190.
doi: 10.1097/SLA.0000000000000868

PMCID: PMC4309752
NIHMSID: NIHMS618905

PREOP-Gallstones: A Prognostic Nomogram for the Management of Symptomatic Cholelithiasis in Older Patients

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Abstract

Go to:

OBJECTIVE AND SUMMARY BACKGROUND DATA

The decision regarding elective cholecystectomy in older patients with symptomatic cholelithiasis is complicated. We developed and validated a prognostic nomogram to guide shared decision-making for these patients.

METHODS

We used Medicare claims (1996–2005) to identify the first episode of symptomatic cholelithiasis in patients >65 who did not undergo hospitalization or elective cholecystectomy within 2.5 months of the episode. We described current patterns of care and modeled their risk of emergent gallstone-related hospitalization or cholecystectomy at two years. Model discrimination and calibration were assessed using a random split sample of patients.

RESULTS

We identified 92,436 patients presenting to the emergency department (ED, 8.3%) or physician's office (91.7%) and who were not immediately admitted. The diagnosis for the initial episode was biliary colic/dyskinesia (65.3%), acute cholecystitis (26.6%), choledocholithiasis (5.7%), or gallstone pancreatitis (2.4%). The 2-year emergent gallstone-related hospitalization rate was 11.1%, with associated in-hospital morbidity and mortality rates of 56.5% and 6.5%. Factors associated with gallstone-related acute hospitalization included male gender, increased age, fewer comorbid conditions, complicated biliary disease on initial presentation, and initial presentation to the ED. Our model was well-calibrated and identified 51% of patients with a <10% risk of 2-year complications and 5.4% with >40% risk (C-statistic 0.69, 95% CI 0.63–0.75).

CONCLUSIONS

Surgeons can use this prognostic nomogram to accurately provide patients with their 2-year risk of developing

gallstone-related complications, allowing patients and physicians to make informed decisions in the context of their symptom severity and its impact on their quality of life.

INTRODUCTION

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Gallstone disease is a leading cause for inpatient admissions for gastrointestinal disease and is the most costly digestive disease in the United States. The cost of treating symptoms and complications related to gallstone disease in the United States is currently estimated to exceed $6.5 billion annually.[1] After an initial episode of biliary colic, 20–40% of patients will experience recurrent episodes.[2–4] Within one year, approximately 14% will develop acute cholecystitis, 5% will develop gallstone pancreatitis, and 5% will develop common bile duct stones.[5–7]

A 2009 Cochrane meta-analysis of randomized controlled trials indicated that early cholecystectomy for symptomatic cholelithiasis is associated with decreased risk for conversion, decreased operative time, and decreased length of stay in the hospital when compared to delayed intervention.[8] Based on these data, the current standard of care for patients presenting with symptomatic cholelithiasis is early, elective cholecystectomy in an effort to avoid gallstone-related complications and costs. However, in older patients the decision to perform elective cholecystectomy is complicated by multiple competing risks. Associated chronic illness increases the morbidity and mortality of elective cholecystectomy. At the same time, older patients are at an increased risk of developing gallstone-related complications.[9–14] Once complications occur, the treatment-related morbidity and mortality increase significantly in this vulnerable population.

The management of older patients who present with symptomatic cholelithiasis has not been well described. Our first objective was to use Medicare claims data to comprehensively describe the trajectory of older patients who are managed nonoperatively after an incident episode of symptomatic cholelithiasis. Our second objective was to develop and validate a risk prediction model that would identify older patients who are at highest risk for recurrent episodes. The ability to provide patients with their individualized risk of developing gallstone-related complications can improve the shared decision-making process in the management of these patients.

METHODS

Go to:

This study was determined to be exempt from review by the Institutional Review Board at the University of Texas Medical Branch.

Data Source

We used a 5% national sample of Medicare claims data from 1995–2007. Medicare claims data include patient demographic information, outpatient visits, physician services, and hospital admissions.[15] Data from Medicare Part A inpatient billing claims (MEDPAR) and Medicare Part B claims, including the Carrier claims and Outpatient Standard Analytic File (SAF) were used.[16]

Cohort Selection

Figure 1 illustrates the cohort selection for the study. We identified all MEDPAR, Outpatient SAF, and Carrier claims for hospital, emergency department, and physician visits with 1) an International Classification of Diseases, 9th Edition, Clinical Modification (ICD-9-CM) primary diagnosis of 574* or 575* or 2) primary diagnosis of acute pancreatitis (ICD-9-CM 577.0) and a secondary diagnosis of ICD-9-CM 574* or 575* as has been done previously.[17] While Medicare data from 1995–2007 were available, we only included incident gallstone cases from 1996–2005. This was done in order to: 1) identify patient comorbidities from the claims data the year prior to the incident diagnosis and 2) to enable us to "follow" all patients via their claims data for at least two years after the date of initial diagnosis. The first claim for symptomatic cholelithiasis was identified for each patient and defined as the incident episode. Patients were included if they were aged 66 years or older and had

Medicare Parts A and B fee-for-service and no HMO for one year prior (to identify incident cases) and two years following the incident claim, or until death. Patients who were admitted to a hospital or underwent cholecystectomy at the time of the incident episode of symptomatic cholelithiasis were excluded. To ensure we were capturing patients with confirmed symptomatic cholelithiasis, patients were excluded if the diagnosis of cholelithiasis was not accompanied by computed tomography (CT) and/or ultrasound (US) in the one month before or after the claim. CT and US were identified in the carrier and outpatient SAF claims files using Current Procedural Terminology codes (Supplemental Table 1).

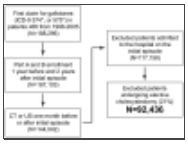

Figure 1

Cohort Selection. Symptomatic cholelithiasis defined by 1) Primary diagnosis of ICD-9-CM code 574 of 575 or 2) Primary diagnosis of acute pancreatitis (577.0) and a secondary diagnosis of 574 or 575. Only patients ≥66 who underwent CT and/or US **...**

We excluded patients who underwent elective cholecystectomy after the initial episode. To define elective cholecystectomy, we searched for any claim for cholecystectomy (see Supplemental Table 1 for ICD-9-CM and CPT codes) following the incident episode that was coded as "elective" in the Medicare type of admission variable. Then we calculated a cumulative incidence curve for elective cholecystectomy. Patients were censored for death and emergency cholecystectomy. A piecewise regression model was used to identify the time point when the cumulative incidence plateaued (inflection point). The location of this inflection point (or joint point) was estimated by nonlinear least squares regression. For elective cholecystectomy, the inflection point was 2.44 months (Fig. 2, 95% CI 2.39, 2.48). We used this inflection point to define elective cholecystectomy for the cohort, and excluded any patient undergoing a cholecystectomy coded as elective within 2.5 months after the incident episode. The final study cohort included 92,436 patients.

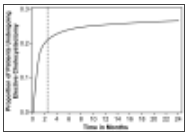

Figure 2

Cumulative incidence curve for elective cholecystectomy for the study cohort using a piecewise regression model (least squares non-linear regression). Patients were censored for death or emergency cholecystectomy. Of these patients undergoing elective **...**

Covariates

We recorded patient demographic characteristics including age, sex, race/ethnicity, Elixhauser comorbidity index, and diagnosis at initial claim for symptomatic cholelithiasis (biliary colic/biliary dyskinesia, acute cholecystitis, common bile duct stones, and gallstone pancreatitis; Table 1). Elixhauser comorbidity index was used as a summary measure for patient comorbidity, as described previously.[18] Type of initial visit (emergency department versus physician office) was also recorded.

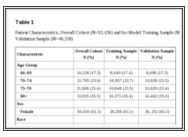

Table 1

Patient Characteristics, Overall Cohort (N=92,436) and for Model Training Sample (N=46,218) and Model Validation Sample (N=46,218)

Description of Trajectory

Patients were followed from the date of initial episode to any gallstone-related event. Potential gallstone-related events included emergent hospitalization, emergent cholecystectomy, delayed elective cholecystectomy (>2.5 months after initial episode), or emergency department/outpatient physician visits with a gallstone-related diagnosis. Emergent admission was identified using MEDPAR inpatient billing claims and defined as any

gallbladder-related claim coded as "emergency" or "urgent" in the type of admission variable. Overall in-hospital morbidity and mortality, perioperative complications, and 30-day operative mortality were calculated for patients who underwent emergent cholecystectomy. Codes used to identify perioperative complications within thirty days of the date of surgery are included in Supplemental Table 1. Operative mortality was defined as death from any cause occurring within thirty days from the date of surgery or a discharge status coded as "Discharged dead." Patients who did not experience any of the above outcomes and did not die were presumed not to have any gallstone-related problems over the two-year period following the initial episode.

Trajectory of Care

Descriptive statistics were used to summarize the sample characteristics at initial presentation and to describe patients within each trajectory of care: 1) patients without further problems, 2) patients who presented with multiple emergency department or physician visits but were not admitted, and 3) patients who required emergent hospitalization.

Risk Prediction Model Creation and Validation

For the purpose of model identification and validation, we randomly split the overall cohort of patients into a training sample (N=46,218) and a validation sample (N=46,218). We used the training sample for model selection and then applied the obtained model parameters to check the performance of the selected model in the validation sample. We developed a Cox proportional hazards regression model to identify factors independently associated with emergent care (admission and/or emergent cholecystectomy) two years after the initial episode, with patients censored for death or elective cholecystectomy after 2.5 months and prior to any emergent hospitalization. Covariates that were included in this model included age group, race/ethnicity, gender, Elixhauser comorbidity index, initial diagnosis (biliary colic, gallstone pancreatitis, common bile duct stones, and acute cholecystitis), and initial visit (emergency vs. outpatient physician). A Cox proportional hazards model was chosen so that patients could be censored for elective cholecystectomy and death.

The findings from this Cox proportional hazards model were used to formulate a prognostic nomogram in R version 3.0.2 (The R Foundation for Statistical Computing, Department of Biostatistics, Vanderbilt University, Nashville, TN) using the package *rms*.[19] We named this model "Predicting Risk of Complications in Older Patients with Gallstones," or the PREOP-Gallstones model. To analyze the discrimination power of the model and correctly distinguish the patients who required emergent care from those who did not need emergent care within two years, we estimated overall C-statistics as described by Uno et al.[20] C-statistics in the setting of a survival analysis can be considered as an expansion of the receiver operating characteristics (ROC) curve.[21] Using regression parameters from our Cox proportional hazards model used in training sample, we estimated the expected probability of requiring emergent care at two years for each patient in the model validation sample. We used modified Hosmer-Lemeshow χ^2 with 9 df to analyze the agreement of predicted probabilities of our risk prediction model to the actual observed outcomes (model calibration).[22] For this purpose, predicted probabilities of requiring emergent care were categorized into deciles and the mean of each decile was compared with the actual observed incidence of emergent care as estimated by Kaplan-Meier analysis. The predicted mean of each decile in the training model sample was compared to the mean observed proportion of patients in the model validation sample who actually required emergent care in a Kaplan-Meier time-to-event analysis.

C-statistics were estimated by using R package 'survC1'[20] and all other statistical analyses were performed using *SAS* version 9.3 (SAS Inc., Cary, NC, USA). Statistical significance was accepted at the $p<0.05$ level.

RESULTS

Go to:

Overall Sample Characteristics (Table 1)

We identified 117,158 patients presenting with an initial episode of symptomatic cholelithiasis; 24,722 (21.1%) underwent elective cholecystectomy within 2.5 months, leaving 92,436 patients who met our inclusion criteria. The mean age was 77.0 ± 7.2 years. The majority of patients were white (87.5%) and female (61.1%). Outpatient evaluation was initially performed in 91.7% of patients, while the remaining 8.3% first presented to the emergency department. The primary visit diagnosis for the incident episode was biliary colic in 65.3%, acute cholecystitis in 26.7%, common bile duct stones in 5.7%, and gallstone pancreatitis in 2.4%.

Description of Trajectory

Figure 2 shows the cumulative incidence of elective cholecystectomy a one year. As described in the methods, elective cholecystectomy was defined as cholecystectomy within 2.5 months of diagnosis based on the inflection point. 77.2% of elective cholecystectomies were performed in the first 2.5 months after the incident episode of symptomatic gallstones.

Of the 92,436 patients who did not undergo early elective cholecystectomy, 10,247 (11.1%) eventually required emergency hospitalization for gallstone-related complications, and 8,508, or 83.0%, of these admitted patients underwent emergency cholecystectomy (Fig. 3). An additional 12,176 patients (13.1%) re-presented to the emergency department or to an outpatient physician at least once over the two years for biliary symptoms but did not require hospitalization or emergent cholecystectomy. 3,704 patients underwent delayed elective cholecystectomy more than 2.5 months after the initial episode. Of these patients, 3.4% had postoperative complications, and perioperative mortality was 0%. Finally, 69,309 patients (71.7%) did not require any emergent gallstone-related intervention or additional visits. 49,483 (53.5%) survived to two years and the remainder died of unrelated causes during the two year follow-up period.

Figure 3
Trajectory of care for Medicare patients with symptomatic cholelithiasis initially managed nonoperatively (N=92,436). 10,247 (11.1%) subsequently required emergent care, 12,176 (13.1%) had recurrent symptoms but did not require hospitalization or surgery, **...**

In-hospital morbidity and mortality were high for the 10,247 patients who presented with emergent hospitalization for gallstone-related complications; 56.5% and 6.1%, respectively. Perioperative morbidity (26.8%) and mortality (1.2%) for the 8,508 patients who underwent emergency cholecystectomy were also elevated.

Prognostic Nomogram Creation and Validation (Figure 4)

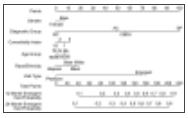

Figure 4
"Predicting Risk of Complications in Older Patients with Gallstones," PREOP-Gallstones model nomogram. To use the nomogram, a vertical line is drawn from each factor to the corresponding position on the "Points" line. Once **...**

The overall cohort was randomly split into equal-sized training and validation samples; sample characteristics and 2-year rates of emergent events were similar for the two samples (Table 1). The training sample was used to generate a Cox proportional hazards model for the development of emergent gallstone-related events (Table 2). Factors independently associated with need for emergency care were older age, white race, male sex, initial visit to emergency room department, and a diagnosis of complicated gallstone disease (gallstone pancreatitis, common bile duct stones, and acute cholecystitis) at initial presentation. Patients with the least comorbidities were also more likely to require emergency care.

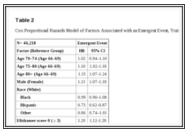

Table 2

Cox Proportional Hazards Model of Factors Associated with an Emergent Event, Training Sample of Patients*

Based on this multivariable model, we developed our model, the PREOP-Gallstones model, which can be used to promote shared decision making (Fig. 4). A prognostic nomogram can be used by clinicians to visually calculate probabilities of an outcome using data based on regression modeling. In using this nomogram, a line is drawn vertically from each factor to the corresponding point. Once all factors and points are tabulated, these points can be added, and then another vertical line is used to determine a patient's 12-month and 24-month risk for developing emergent gallstone-related complications.

When applied to the validation sample, the C statistic for our model was 0.69 (95% confidence interval, 0.63 to 0.75). Figure 5 shows the calibration plot comparing predicted deciles of risk of emergent events at 2 years and actual observed risk for the training sample. Our model estimates closely approximated the observed mean frequencies of emergent care. Our model was able to accurately identify the 10% of the older population who had a greater than 45% risk of developing gallstone-related complications and 50% of the population whose risk was <10%. Model specificity and sensitivity were 71.2% and 91%, respectively.

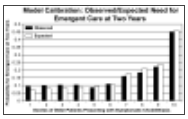

Figure 5

Model calibration results. The observed-to-expected probabilities for patients requiring emergent care (hospitalization and/or cholecystectomy) at two years. The graph illustrates that there was little difference between the expected calculated probability **...**

DISCUSSION

Go to:

We used a large population-based cohort to describe the trajectory of care in older patients presenting with an initial episode of symptomatic cholelithiasis who did not undergo elective cholecystectomy. While cholecystectomy is the standard of care for patients presenting with symptomatic cholelithiasis, we observed that many older patients did not undergo elective cholecystectomy. As in prior studies,[2,23,24] the majority of older patients with symptomatic cholelithiasis in our study who did not undergo elective cholecystectomy did not ultimately experience complications that required hospitalization or surgery. However, nearly one-third required delayed elective cholecystectomy, had ongoing symptoms, or required emergency gallstone-related hospitalization, and morbidity and in-hospital mortality high for these patients who eventually required emergent care. Based on these data, we developed the PREOP-Gallstones model, a nomogram that reliably predicted patients with an over 40% 2-year risk of developing gallstone-related complications (approximately 10% of the cohort) and an additional 50% of patients with less than 10% 2-year risk.

Our study is the first to incorporate easily measurable characteristics into a risk prediction model to identify the likelihood for emergent biliary-related hospitalization for older patients with biliary disease. A prognostic nomogram visually depicts the findings of multivariate modeling, has been previously implemented into decision modeling for surgical patients,[25,26] and has been suggested to enhance communication between patients and practitioners.[27–29] Unlike complex statistical models, nomograms can be easily integrated into the patient-practitioner encounter and thereby improve the shared decision-making process. The PREOP-Gallstones model included variables such as age, race/ethnicity, gender, number of comorbidities, initial diagnosis, and location for initial visit, and was able to identify a group of patients at high-risk (>40%) for subsequent gallstone-related emergent hospitalizations and a group at low risk. Practitioners can use these readily-available characteristics to counsel each individual patient on their expected risks for requiring emergency care.

The characteristics associated with emergent biliary complications were not unanticipated. Initial presentation to

the emergency department and complicated biliary disease, factors that are likely proxies for disease severity, were also independent risk factors for subsequent hospitalization. Older age has been previously suggested to be a risk factor for persistent biliary symptoms after an initial attack.[23] Increased comorbidity, which for these older patients is a threat for a competing risk of early death, was a protective factor for subsequent biliary complications. While this finding appears counterintuitive, the number of comorbidities in this vulnerable cohort of older patients likely limited their life expectancy. Many of these patients with multiple comorbidities may have died from their chronic medical conditions such as heart disease, before they could develop symptoms of gallstone disease. This is further supported by the relatively high 22.9% mortality rate at two years we observed for the overall cohort, and the dramatically elevated 2-year mortality rate of 40.4% for those patients with 3 or more Charlson comorbidities. Finally, we observed, as others have, that male sex is an indicator for increased biliary disease severity.[30–36] The male predominance in emergent biliary surgery has been suggested to be related to social factors (men may be less likely follow medical advice),[31] biochemical factors (female hormones may sensitize women to the inflammation of cholecystitis), anatomic factors, or less frequent use of medical services amongst men.[37]

The relative contributions for these factors should also be placed in the appropriate context. The two factors most strongly associated with an emergent presentation were initial patient presentation to the emergency department and a diagnosis of complicated biliary disease. As the nomogram illustrates, a patient presenting with either of these factors has a dramatically elevated risk for emergent biliary complications at two years (15–25%). In contrast, a patient presenting with the cumulative burden of all the other factors combined but without complicated biliary disease or emergent presentation would have only an approximate 10% risk at two years. As a result, the PREOP-Gallstones model could be validated and the practical utility demonstrated by future studies using electronic medical records in clinical practice settings with additional pertinent clinical findings, such as ultrasound characteristics or patient laboratory values.

Our findings also suggest that elective cholecystectomy is underused in a cohort of older patients with symptomatic cholelithiasis who are more likely to experience disease progression than younger patients. The reasons for this disparity are multi-factorial, but one contributing factor is the absence of a solid evidence-base on which to counsel patients. The PREOP-Gallstones model fills this knowledge gap for both patients and practitioners.

Our study has several limitations. Our goal was to review current practice patterns and identify risk factors for developing complications related to gallstones, to determine if all older patients do in fact need cholecystectomy after an initial episode, and if they do not, who would most benefit. As such, we excluded patients admitted to the hospital on the initial episode, as these were patients with severe enough symptoms to require admission. We also excluded patients who underwent an early elective cholecystectomy in the initial 2.5 months after diagnosis (N=24,722), representing only 21% of the study population. For these patients, the decision to perform early cholecystectomy was likely dictated by patient disease severity, patient or practitioner preference, or any number of reasons that our analysis cannot capture. We suspect that the rates of emergent admission would be higher if these 21% did not undergo cholecystectomy. As a result, our model findings only apply to a marginal population of patients in whom the decision to perform cholecystectomy can be difficult.

In addition, the model C-statistic would suggest a marginal discriminatory ability, but our calibration results indicate that these findings are likely due to poor discrimination amongst patients in the lowest deciles of requiring emergent care. However, within each decile, prediction was very accurate, and our model was able to accurately identify the 10% of patients who have a >40% risk of developing emergent biliary complications (high specificity) and over 50% who have a less than 10% 2-year risk.

In addition, the PREOP-Gallstones model is based on administrative data that cannot capture practitioner or patient intent. Some patients may have elected to forego surgery counter to recommendations, or there may have been indications for delaying surgery such as need for anti-platelet therapy for a recent percutaneous coronary

intervention. In other cases, patients may have been scheduled for elective cholecystectomy but their disease progressed in the interim. Given the model limitations, physicians should consider the results in the context of each individual patient's symptom severity, presentation, and preferences. For instance, while one patient may view a 10% risk for emergent care as prohibitive, another may view this as minute, and as a result surgeons should work with patients to develop the optimal individualized treatment plan for them. In this manner our model can be used in uncertain cases to counsel patients that are at high-risk for disease progression and who may benefit most from early elective cholecystectomy. Conversely, our model was able to generally identify certain patients that have low risk (<10%) for subsequent biliary complications, and elective cholecystectomy may not be necessary for this group. Further validation of our model with other samples may be needed to illustrate its utility in this regard.

The PREOP-Gallstones model will enable internists, hospitalists, primary care physicians, and surgeons to use readily identifiable patient characteristics to quantify an individualized risk score of requiring emergent biliary care. Practitioners can use these data to accurately provide patients with their 2-year risk of developing gallstone-related complications at the point of care, allowing patients to make informed decisions in the context of their symptom severity and its impact on their quality of life. This approach has the potential to mitigate the morbidity and mortality of emergency care and reduce unnecessary cholecystectomy for patients who are unlikely to benefit.

Supplementary Material

Go to:

SDC Table

Click here to view.(42K, doc)

Acknowledgments

Go to:

Funding: Supported by grants from the UTMB Clinical and Translational Science Award #UL1TR000071, NIH T-32 Grant # 5T32DK007639, and AHRQ Grant # 1R24HS022134

References

Go to:

1. Shaffer EA. Epidemiology and risk factors for gallstone disease: has the paradigm changed in the 21st century? Curr Gastroenterol Rep. 2005;7:132–140. [PubMed]

2. Thistle JL, Cleary PA, Lachin JM, et al. The natural history of cholelithiasis: the National Cooperative Gallstone Study. Ann Intern Med. 1984;101:171–175. [PubMed]

3. Epari KP, Mukhtar AS, Fletcher DR, et al. The outcome of patients on the cholecystectomy waiting list in Western Australia 1999–2005. ANZ J Surg. 2010;80:703–709. [PubMed]

4. Rutledge D, Jones D, Rege R. Consequences of delay in surgical treatment of biliary disease. Am J Surg. 2000;180:466–469. [PubMed]

5. Gurusamy KS, Davidson BR. Surgical treatment of gallstones. Gastroenterol Clin North Am. 2010;39:229–244. viii. [PubMed]

6. McSherry CK, Ferstenberg H, Calhoun WF, et al. The natural history of diagnosed gallstone disease in symptomatic and asymptomatic patients. Ann Surg. 1985;202:59–63. [PMC free article] [PubMed]

7. Somasekar K, Shankar PJ, Foster ME, et al. Costs of waiting for gall bladder surgery. Postgrad Med J. 2002;78:668–669. [PMC free article] [PubMed]

8. Gurusamy KS, Samraj K, Fusai G, et al. Early versus delayed laparoscopic cholecystectomy for biliary colic. Cochrane Database Syst Rev. 2008:CD007196. [PubMed]

9. Arthur JD, Edwards PR, Chagla LS. Management of gallstone disease in the elderly. Ann R Coll Surg Engl. 2003;85:91–96. [PMC free article] [PubMed]

10. Dubecz A, Langer M, Stadlhuber RJ, et al. Cholecystectomy in the very elderly--is 90 the new 70? J Gastrointest Surg. 2012;16:282–285. [PubMed]

11. Hazzan D, Geron N, Golijanin D, et al. Laparoscopic cholecystectomy in octogenarians. Surg Endosc. 2003;17:773–776. [PubMed]

12. Lo CM, Lai EC, Fan ST, et al. Laparoscopic cholecystectomy for acute cholecystitis in the elderly. World J Surg. 1996;20:983–986. discussion 987. [PubMed]

13. Maxwell JG, Tyler BA, Rutledge R, et al. Cholecystectomy in patients aged 80 and older. Am J Surg. 1998;176:627–631. [PubMed]

14. Pavlidis TE, Marakis GN, Symeonidis N, et al. Considerations concerning laparoscopic cholecystectomy in the extremely elderly. J Laparoendosc Adv Surg Tech A. 2008;18:56–60. [PubMed]

15. [Accessed December, 2012];Research, Statistics, Data & Systems. Available at: http://www.cms.gov/Research-Statistics-Data-and-Systems/Research-Statistics-Data-and-Systems.html.

16. Center for Medicare & Medicaid Services. [Accessed December, 2012]; Available at: http://www.cms.gov/

17. Riall TS, Zhang D, Townsend CM, et al. Failure to perform cholecystectomy for acute cholecystitis in elderly patients is associated with increased morbidity, mortality, and cost. J Am Coll Surg. 2010;210:668–677. 677–679. [PMC free article] [PubMed]

18. van Walraven C, Austin PC, Jennings A, et al. A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. Med Care. 2009;47:626–633. [PubMed]

19. Harrell F. rms: Regression Modeling Strategies.: R package version 4.1–1. 2014

20. Uno H, Cai T, Pencina MJ, et al. On the C-statistics for evaluating overall adequacy of risk prediction procedures with censored survival data. Stat Med. 2011;30:1105–1117. [PMC free article] [PubMed]

21. Harrell F, Lee K, Califf R. Tutorials in Biostatistics: Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med. 1996;15:361–387. [PubMed]

22. D'Agostino R, Nam B. Evaluation of the performance of survival analysis models: discrimination and calibration measures. Amsterdam, Netherlands: Elsevier; 2004.

23. Festi D, Reggiani ML, Attili AF, et al. Natural history of gallstone disease: Expectant management or active treatment? Results from a population-based cohort study. J Gastroenterol Hepatol. 2010;25:719–724. [PubMed]

24. Schmidt M, Søndenaa K, Vetrhus M, et al. A randomized controlled study of uncomplicated gallstone disease with a 14-year follow-up showed that operation was the preferred treatment. Dig Surg. 2011;28:270–276. [PubMed]

25. Kiran RP, Attaluri V, Hammel J, et al. A novel nomogram accurately quantifies the risk of mortality in elderly patients undergoing colorectal surgery. Ann Surg. 2013;257:905–908. [PubMed]

26. Tseng WH, Yang X, Wang H, et al. Nomogram to predict risk of 30-day morbidity and mortality for patients with disseminated malignancy undergoing surgical intervention. Ann Surg. 2011;254:333–338. [PubMed]

27. Albert JM, Liu DD, Shen Y, et al. Nomogram to predict the benefit of radiation for older patients with breast cancer treated with conservative surgery. J Clin Oncol. 2012;30:2837–2843. [PMC free article] [PubMed]

28. Grobman WA, Stamilio DM. Methods of clinical prediction. Am J Obstet Gynecol. 2006;194:888–894. [PubMed]

29. Kattan MW, Yu C, Salomon L, et al. Development and validation of preoperative nomogram for disease recurrence within 5 years after laparoscopic radical prostatectomy for prostate cancer. Urology. 2011;77:396–401. [PubMed]

30. Russell JC, Walsh SJ, Reed-Fourquet L, et al. Symptomatic cholelithiasis: a different disease in men? Connecticut Laparoscopic Cholesystectomy Registry. Ann Surg. 1998;227:195–200. [PMC free article] [PubMed]

31. Sanabria JR, Gallinger S, Croxford R, et al. Risk factors in elective laparoscopic cholecystectomy for conversion to open cholecystectomy. J Am Coll Surg. 1994;179:696–704. [PubMed]

32. Botaitis S, Polychronidis A, Pitiakoudis M, et al. Does gender affect laparoscopic cholecystectomy? Surg Laparosc Endosc Percutan Tech. 2008;18:157–161. [PubMed]

33. Waage A, Nilsson M. Iatrogenic bile duct injury: a population-based study of 152 776 cholecystectomies in the Swedish Inpatient Registry. Arch Surg. 2006;141:1207–1213. [PubMed]

34. Sinha S, Hofman D, Stoker DL, et al. Epidemiological study of provision of cholecystectomy in England from 2000 to 2009: retrospective analysis of Hospital Episode Statistics. Surg Endosc. 2013;27:162–175. [PubMed]

35. Harboe KM, Bardram L. The quality of cholecystectomy in Denmark: outcome and risk factors for 20,307 patients from the national database. Surg Endosc. 2011;25:1630–1641. [PubMed]

36. Giger UF, Michel JM, Opitz I, et al. Risk factors for perioperative complications in patients undergoing laparoscopic cholecystectomy: analysis of 22,953 consecutive cases from the Swiss Association of Laparoscopic and Thoracoscopic Surgery database. J Am Coll Surg. 2006;203:723–728. [PubMed]

37. Pinkhasov RM, Wong J, Kashanian J, et al. Are men shortchanged on health? Perspective on health care utilization and health risk behavior in men and women in the United States. Int J Clin Pract. 2010;64:475–487. [PubMed]

J Gastrointest Surg (2009) 13:312–317
DOI 10.1007/s11605-008-0729-y

ORIGINAL ARTICLE

Is Complicated Gallstone Disease Preceded by Biliary Colic?

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Received: 20 August 2008 / Accepted: 6 October 2008 / Published online: 24 October 2008

Abstract
Introduction Cholecystectomy in cases of "warning" episodes of biliary colic may prevent biliary pancreatitis. We aimed to determine which proportion of patients with biliary pancreatitis, compared to other complicated and uncomplicated symptomatic gallstone disease, experienced "warning" episodes of colic and why these episodes did not lead to early cholecystectomy.
Patients and methods One hundred seventy-five patients with complicated gallstone disease [pancreatitis (n=53), symptomatic common bile duct (CBD) stones (n=64), and acute cholecystitis (n=58)] and 175 patients with symptomatic uncomplicated gallstones were interviewed at admission.
Results Fifty-seven percent (100 of 175) of patients with complicated disease (95% confidence interval=50–65%) experienced "warning" episodes of biliary colic (pancreatitis 58%, CBD stones 67%, cholecystitis 45%) vs 96% (164 of 175) in uncomplicated disease. Eighty-seven percent of patients with "warning" episodes and complicated disease experienced patient's and general practitioner's delays. General practitioner's delay was more frequent if pain was located in the epigastric region compared to the right upper quadrant (51% vs 38%, P=0.03).
Conclusions Half of patients with biliary pancreatitis experience "warning" episodes of biliary colic, similar to other gallstone complications. In symptomatic patients, complications are often not prevented because of significant delays in diagnosis and treatment.

Keywords Acute pancreatitis · Cholecystectomy · Cholecystitis · Symptoms · Gallstone

Part of this work was presented at the annual meeting of the American Gastroenterological Association (Chicago, May 2005) and published in abstract form in Gastroenterology 2005; 128: Suppl 2, A-79.

MGHB, NGV, and KJvE participated in the design of the study, analysis, and interpretation of data. MGHB drafted the manuscript. All authors participated in revising the article for important intellectual content. All authors approved the final version.

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Introduction

Acute biliary pancreatitis is associated with significant morbidity and a mortality rate of 5%.[1] The incidence of biliary pancreatitis is increasing with 5% per year.[2,3] It is estimated that, in developed countries, at least one in every ten adults carries gallstones.[4–6] In asymptomatic gallstone carriers, the annual risk of developing biliary pancreatitis is up to 0.2%.[7–9] Furthermore, there is a 0.2% annual risk of developing common bile duct (CBD) stones and a 0.3% risk of acute cholecystitis.[10,11] In symptomatic gallstone carriers, the risks of developing complications are much higher.[12]

Although cholecystectomy in asymptomatic gallstone carriers would prevent symptoms and complicated gallstone disease, (laparoscopic) cholecystectomy is also associated with morbidity and even mortality.[13] In a decision analysis study using a Markov model and Monte Carlo simulations, we found that, in most health care situations, prophylactic cholecystectomy in asymptomatic gallstone carriers did not improve outcome.[14,15] Strategies to prevent biliary pancreatitis should, therefore, rather focus on the early cholecystectomy in symptomatic carriers.[16–18] Surprisingly, it is virtually unknown what proportion of patients with biliary pancreatitis is symptomatic prior to the onset of the complication. Also, it is unknown to what extent patient's and doctor's delay due to poor recognition of gallstone-related symptoms in symptomatic patients are present.[19]

The aims of the current study were to investigate in a large group of patients with biliary pancreatitis and other complicated as well as uncomplicated symptomatic gallstone disease: (1) the occurrence of "warning" episodes of biliary colic and (2) patient's and doctor's delays in symptomatic patients.

Patients and Methods

Patients

All consecutive patients admitted with a first episode of biliary pancreatitis or CBD obstruction or acute cholecystitis in a university medical center and an affiliated large teaching hospital in the period 2003–2005 were eligible for inclusion. A parallel consecutive cohort of patients who visited the outpatient clinic because of uncomplicated symptomatic gallstone disease served as a disease–control group. Patients who refused informed consent, were under 18 years of age, with previous cholecystectomy, with a history of complicated gallstone disease, or with gallbladder carcinoma were excluded. Patients were also excluded if adequate history taking was not possible (due to inability to speak Dutch, German, or English or mental disability). All patients gave informed consent.

Data Collection

From all enrolled patients, a detailed history was taken at admission by one of two investigators (MGHB, NGV). When patients were considered to be too ill or painful for adequate history taking, they were visited again after their condition had improved. The following data were collected: age, sex, date of first biliary colic, visit to general practitioner for episodes of biliary colic, referral for ultrasound or specialist evaluation by general practitioner, numbers of episodes of biliary colic. Results of upper gastrointestinal endoscopy and presence on the waiting list for cholecystectomy at the time of the complication were retrieved from hospital records. Hospital stay, potential complicated course of the disease, and in-hospital mortality were obtained from hospital records.

Definitions

For the purpose of this study, complicated gallstone disease was restricted to acute biliary pancreatitis, symptomatic CBD stones, and acute cholecystitis. Acute pancreatitis was defined as severe abdominal pain of acute onset and elevated serum amylase or lipase level at least three times the upper limit of normal. A biliary genesis was assumed when, in the absence of alcohol abuse or other factors known to predispose to pancreatitis, gallbladder/CBD stones or sludge were detected by abdominal ultrasonography or endoscopic retrograde cholangiopancreatography (ERCP), serum liver enzymes and/or bilirubin were elevated, or when the CBD was dilated (>8 mm).[14] Symptomatic CBD stones were defined as the presence of abdominal symptoms, fever, or jaundice in combination with CBD/gallbladder stones or sludge detected by ultrasonography in combination with dilation of the CBD (>8 mm) or an elevation of serum liver enzymes and bilirubin with the result that ERCP was required. Serum amylase and lipase values had to be normal. Acute cholecystitis was defined as biliary pain of at least 2-h duration with fever and upper abdominal pain in the presence of stones or sludge in the gallbladder detected on abdominal ultrasonography with normal serum amylase and lipase levels. The diagnosis "acute cholecystitis" was always confirmed during surgery. A biliary colic was defined as one or more episodes of upper abdominal pain, lasting at least 30 min but less than 6 h.[20] Uncomplicated symptomatic gallstone disease was defined as one or more episodes of biliary colic in the absence of complicated gallstone disease as defined above. Radiating pain and urge to move were not considered mandatory.

Since biliary pain may also occur at the onset of a complication, the patient was required to have had a symptom-free interval of at least 7 days between the first colic and the complication before classification in the group

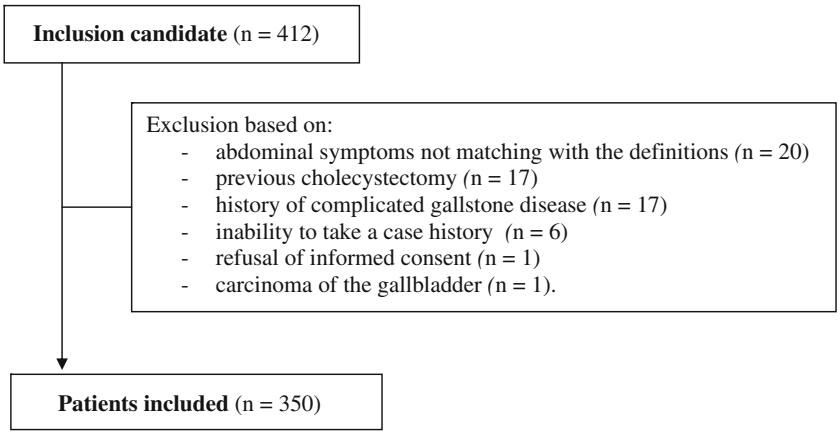

Figure 1 Flow diagram of gallstone patients referred for pain of potentially biliary origin.

complicated disease with "warning" episodes of colic was allowed. General practitioner delay was defined as at least one visit to a general practitioner because of a biliary colic without referral for ultrasound or to a specialist for further evaluation or, in case of previous diagnosis of gallbladder stones, for cholecystectomy. Patient delay was defined as at least one biliary colic without subsequent visit within 7 days to a general practitioner or emergency department.

Statistical Analysis

Categorical data were compared using Pearson's chi square or Fisher's exact test as appropriate. If appropriate, odds ratios (OR) and 95% confidence intervals (95%CI) are provided. All continuous data are expressed as medians with range. Continuous variables were compared using the Mann–Whitney *U* test, Kruskal–Wallis, or analysis of variance (ANOVA), as appropriate. No correction for multiple testing was applied. When probability was <0.05 for the Kruskal–Wallis test, the Mann–Whitney *U* test was used as a post hoc test to compare the three groups of patients with complicated gallstone disease with the symptomatic group. For the ANOVA test, the Fisher's least significant difference test was used as a post hoc test in cases of probability of <0.05 with ANOVA. In cases of positively skewed, non-Gaussian data, the 75th percentile (P75) is represented as upper range. Statistical significance was defined as two-tailed P value< 0.05. All statistical analyses were performed using SPSS version 12.01 (SPSS, Chicago, IL, USA).

Results

Patients

A total of 412 patients were screened for inclusion. Reasons for nonenrollment are summarized in Fig. 1. Finally, 350 consecutive patients were included; 175 consecutive patients with first clinical presentation of gallstone complications: acute biliary pancreatitis (n=53), symptomatic CBD stones (n=64), and acute cholecystitis (n=58) and 175 consecutive patients scheduled for elective cholecystectomy because of uncomplicated symptomatic gallstone disease. Patient characteristics are shown in Table 1. Patients with complicated gallstone disease were more often males, were older, and had less often a family history of gallstone disease compared to patients with uncomplicated symptomatic gallstone disease. Eight patients (5%) in

Table 1 Characteristics of Patients with Complicated and Uncomplicated, Symptomatic Gallstone Disease

	Biliary pancreatitis (n=53)	Symptomatic CBD stones (n=64)	Acute cholecystitis (n=58)	Uncomplicated disease (n=175)	P value
Age, years (range)	50 (24–82)	56 (19–92)	62 (24–90)	48 (20–86)	<0.01[a]
Males, n (%)	26 (49)	22 (34)	31 (53)	40 (23)	<0.01[b]
Body mass index, kg/m^2 (range)	28 (17–45)	25 (18–58)	25 (20–49)	27 (18–43)	<0.01[c]
Biliary colics prior to diagnosis, n (%)	31 (58)	43 (67)	26 (45)	164 (94)	<0.01[d]

[a] Difference between patients with CBD stones and acute cholecystitis vs uncomplicated disease
[b] Difference between patients with acute pancreatitis and acute cholecystitis vs uncomplicated disease
[c] Difference between patients with CBD stones vs uncomplicated disease
[d] Difference between patients with acute biliary pancreatitis, CBD stones, and acute cholecystitis vs uncomplicated disease

Table 2 Characteristics of Biliary Pain in Patients with "Warning" Biliary Symptoms

	Biliary pancreatitis (*n*=53)	Symptomatic CBD stones (*n*=64)	Acute cholecystitis (*n*=58)	Uncomplicated disease (*n*=175)	*P* value
No of colics (min-P75)	5 (1–18)	5 (1–10)	5 (1–16)	5 (1–13)	0.64
With urge to move (min-P75)	2 (1–10)	2 (1–8)	3 (1–10)	3 (1–10)	0.91
Maximum point of pain					
Right upper quadrant	30	33	54	50	0.15
Epigastric region	67	63	42	49	
Other	3	3	4	1	
Radiation of pain					
Only right flank	7	10	15	14	0.28
Circular band	63	63	66	72	
No radiation of pain	30	27	19	14	
Nausea during colic	65	78	58	76	0.31
Vomiting during colic	48	60	46	48	0.41
Taking pain medication for colics	48	50	65	66	0.12

Values are percentages unless mentioned otherwise

the complicated gallstone disease groups had developed a complication while awaiting elective cholecystectomy for a median of 24 days (range 3–75 days).

"Warning" Episodes of Biliary Colic

Of the patients with complicated gallstone disease, 57% (100 of 175, 95%CI=50–65%) experienced "warning" episodes of biliary colic (biliary pancreatitis 58%, symptomatic CBD stones 67%, and cholecystitis 45%, P=0.04; Table 1). Patients with symptomatic CBD stones had "warning" episodes more often than patients with cholecystitis (P=0.01). Patients with biliary pancreatitis did not differ in the incidence of "warning" episodes of biliary colic from patients with CBD stones and/or cholecystitis. As expected, patients with uncomplicated symptomatic disease more often experienced "warning" episodes of biliary colic (94%, 164 of 175) than patients with complicated disease (Table 1).

"Warning" episodes of colic were experienced in the epigastric region by 53% of patients. Although patients with pancreatitis and symptomatic CBD stones predominantly experienced epigastric pain (rather than pain in the right upper quadrant), the difference with acute cholecystitis and symptomatic uncomplicated gallstones was not statistically significant (Table 2).

Delays in Patients with "Warning" Episodes of Colic

Of the patients with complicated gallstone disease and "warning" episodes of colic, 87% of patients (87 of 100) experienced patient's and/or general practitioner's delays (Table 3). Patients with a "warning" colic experienced more doctor's delay if the maximum pain was located in the epigastric region (51%, 70 of 136) compared to the right upper quadrant (38%, 45 of 118, P=0.03). Patient delay was not associated with the location of pain (P=0.39).

Table 3 Delays in Diagnosis and Treatment of Gallstone Patients with "Warning" Colics

	Biliary pancreatitis (*n*=53)	Symptomatic CBD stones (*n*=64)	Acute cholecystitis (*n*=58)	Uncomplicated disease (*n*=175)	*P* value
Days between first colic and diagnosis (min-P75)	243 (9–709)	93 (7–305)	197 (7–885)	176 (7–568)	0.15
Delay	84	91	85	70	0.03[a]
Patient delay[b]	42	42	31	40	0.80
Doctor delay[b]	48	58	58	40	0.11
Known gallstone carrier for at least 1 month	32	29	29	55	0.002[c]
Awaiting cholecystectomy at time of complication	13	7	4	–	0.45

Values are percentages unless mentioned otherwise
[a] Difference between patients with CBD stones vs uncomplicated disease
[b] Patients may experience both patient and doctor delay
[c] Difference between patients with acute pancreatitis, CBD stones, and acute cholecystitis vs uncomplicated disease

Upper Gastrointestinal Endoscopy

Fifty-one patients (15%) underwent endoscopy of the upper gastrointestinal tract because of upper abdominal pain prior to the diagnosis of (un)complicated gallstone disease. In eight patients (16%), minor abnormalities (gastritis or esophagitis grade A) were detected during endoscopy.

Outcome

Ten out of 53 (19%) patients with biliary pancreatitis developed necrotizing pancreatitis requiring a median hospital stay of 40 days (range 8–143 days). Six patients developed (multi)organ failure and were admitted to the intensive care unit. Five of these six and one other patient ultimately underwent surgical necrosectomy for infected necrotizing pancreatitis, albeit without mortality. Four of the ten patients with necrotizing pancreatitis had experienced a "warning" colic, and all four developed infected necrotizing pancreatitis requiring surgical intervention (median hospital stay 130 days). None of these patients died. One patient died after elective cholecystectomy for uncomplicated, symptomatic gallstone disease. Total in-hospital mortality was 0.3% (1 of 350).

Discussion

This study is the first to evaluate the incidence of "warning" biliary colic and the extent of patient and general practitioner delay in patients admitted for biliary pancreatitis and other forms of complicated gallstone disease. The most important findings were that approximately half of patients with pancreatitis had experienced (a median of 5) "warning" episodes of biliary colic during a period of 5 months prior to onset of pancreatitis, very similar to other complicated gallstone diseases. In the majority of these patients, various delays had occurred, which were slightly but significantly more often observed in patients with complicated than with uncomplicated gallstone disease. Up to 40% of patients did not visit their general practitioner after a biliary colic. In addition, patients who visited the general practitioner because of biliary symptoms were often not referred for ultrasound, further specialist evaluation, or surgery. Particularly, epigastric localization of pain, as experienced by over half of gallstone patients in the present series, was associated with general practitioner delay. In patients with epigastric localization of clear episodes of biliary colic, general practitioners frequently consider gastric conditions as the underlying cause. In contrast, patients apparently exhibit no higher frequency of visits to their general practitioners for gallstone-related right upper quadrant pains vs epigastric pains since, in the current study, location of the pain was not associated with patient delays.

This study presents data on a large group of patients collected over a relatively short period of time, which minimizes potential effects of shifts in treatment protocols. The optimal study design would have been a prospective cohort series in asymptomatic gallstone carriers. However, due to the low annual incidence of complicated gallstone disease in asymptomatic gallstone carriers (approximately 0.7%), some 25,000 gallstone carriers would have to be followed up for a year in order to identify 175 patients with complicated gallstone disease as included in the present series. Although a prospective study design would minimize "recall bias," the authors feel that such bias is not likely to have played a major role in this series due to the generally vivid recollection of the intense experience of a biliary colic in our patients.

The purpose of including in the present study a group of symptomatic uncomplicated gallstone patients was not to compare them with the complicated patients for frequency of preceding colics (a priori approaching 100% in the symptomatic uncomplicated group). Rather, we aimed to compare patient's and doctor's delays in these groups. In line with the present findings, previous screening studies demonstrated that mid-upper abdominal pain occurs with equal frequency as right upper abdominal pain in patients with symptomatic gallstones.[17,21] We are aware of one other study that had addressed "warning" episodes of colic in patients with complicated gallstone disease in a retrospective survey of a state-wide database in California. Similar to our findings, approximately half of the patients with complicated gallstone disease in that study had experienced episodes of biliary colic during a period of 142 days prior to cholecystectomy.[22] The authors did not assess the reasons for delayed surgery in these patients. In line with the current data, advanced age and male gender were previously found to be associated with complicated gallstone disease.[14].

Several conclusions and recommendations can be drawn from the present study. First, approximately half the patients with biliary pancreatitis and other complicated gallstone disease do not experience "warning" episodes of biliary colic. In these patients, complications cannot be prevented by a policy of "early cholecystectomy in cases of preceding episodes of colic." Second, patient delay is common and may be reduced by increasing the awareness of the general public for the "warning" aspect of abdominal colicky pain. Third, general practitioner delay is common and may be reduced by increasing awareness of the relation between epigastric pain and gallstone disease. Fourth, the waiting time for elective cholecystectomy should be kept to a minimum in order to guarantee early intervention after diagnosis of "warning" episodes of colic in patients who are fit enough to undergo cholecystectomy.

Acknowledgements MGH Besselink and NG Venneman are MD-medical research trainees for The Netherlands Organization for Health Research and Development (ZonMw, grant numbers 920-03-368 and 920-03-232).

References

1. UK Working Party on Acute Pancreatitis. UK guidelines for the management of acute pancreatitis. Gut 2005;54(Suppl 3):iii1–iii9. doi:10.1136/gut.2004.057026.
2. Frey CF, Zhou H, Harvey DJ, et al. The incidence and case-fatality rates of acute biliary, alcoholic, and idiopathic pancreatitis in California, 1994–2001. Pancreas 2006;33:336–344. doi:10.1097/01.mpa.0000236727.16370.99.
3. Yadav D, Lowenfels AB. Trends in the epidemiology of the first attack of acute pancreatitis: a systematic review. Pancreas 2006;33:323–330. doi:10.1097/01.mpa.0000236733.31617.52.
4. Diehl AK. Epidemiology and natural history of gallstone disease. Gastroenterol Clin North Am 1991;20:1–19.
5. Heaton KW, Braddon FE, Mountford RA, et al. Symptomatic and silent gall stones in the community. Gut 1991;32:316–320. doi:10.1136/gut.32.3.316.
6. Shaffer EA. Gallstone disease: epidemiology of gallbladder stone disease. Best Pract Res Clin Gastroenterol 2006;20:981–996. doi:10.1016/j.bpg.2006.05.004.
7. Chwistek M, Roberts I, Amoateng-Adjepong Y. Gallstone pancreatitis: a community teaching hospital experience. J Clin Gastroenterol 2001;33:41–44. doi:10.1097/00004836-200107000-00010.
8. Halvorsen FA, Ritland S. Acute pancreatitis in Buskerud County, Norway. Incidence and etiology. Scand J Gastroenterol 1996;31:411–414. doi:10.3109/00365529609006419.
9. Persson GE. Expectant management of patients with gallbladder stones diagnosed at planned investigation. A prospective 5- to 7-year follow-up study of 153 patients. Scand J Gastroenterol 1996;31:191–199. doi:10.3109/00365529609031985.
10. Friedman GD, Raviola CA, Fireman B. Prognosis of gallstones with mild or no symptoms: 25 years of follow-up in a health maintenance organization. J Clin Epidemiol 1989;42:127–136. doi:10.1016/0895-4356(89)90086-3.
11. McSherry CK, Ferstenberg H, Calhoun WF, et al. The natural history of diagnosed gallstone disease in symptomatic and asymptomatic patients. Ann Surg 1985;202:59–63. doi:10.1097/00000658-198507000-00009.
12. Portincasa P, Moschetta A, Petruzzelli M, et al. Gallstone disease: symptoms and diagnosis of gallbladder stones. Best Pract Res Clin Gastroenterol 2006;20:1017–29. doi:10.1016/j.bpg.2006.05.005.
13. Keus F, de Jong JA, Gooszen HG, et al. Laparoscopic versus open cholecystectomy for patients with symptomatic cholecystolithiasis. Cochrane Database Syst Rev 2006, 4:CD006231.
14. Venneman NG, Buskens E, Besselink MG, et al. Small gallstones are associated with increased risk of acute pancreatitis: potential benefits of prophylactic cholecystectomy. Am J Gastroenterol 2005;100:2540–2550. doi:10.1111/j.1572-0241.2005.00317.x.
15. Ransohoff DF, Gracie WA, Wolfenson LB, et al. Prophylactic cholecystectomy or expectant management for silent gallstones. A decision analysis to assess survival. Ann Intern Med 1983;99:199–204.
16. Salman B, Yuksel O, Irkorucu O, et al. Urgent laparoscopic cholecystectomy is the best management for biliary colic. A prospective randomized study of 75 cases. Dig Surg 2005;22:95–99. doi:10.1159/000085300.
17. Venneman NG, Besselink MG, Keulemans YC, et al. Ursodeoxycholic acid exerts no beneficial effect in patients with symptomatic gallstones awaiting cholecystectomy. Hepatology 2006;43:1276–1283. doi:10.1002/hep.21182.
18. Rutledge D, Jones D, Rege R. Consequences of delay in surgical treatment of biliary disease. Am J Surg 2000;180:466–469. doi:10.1016/S0002-9610(00)00520-1.
19. Romero Y, Thistle JL, Longstreth GF, et al. A questionnaire for the assessment of biliary symptoms. Am J Gastroenterol 2003;98:1042–1051. doi:10.1111/j.1572-0241.2003.07430.x.
20. Behar J, Corazziari E, Guelrud M, et al. Functional gallbladder and sphincter of oddi disorders. Gastroenterology 2006;130:1498–1509. doi:10.1053/j.gastro.2005.11.063.
21. Thijs C, Knipschild P. Abdominal symptoms and food intolerance related to gallstones. J Clin Gastroenterol 1998;27:223–231. doi:10.1097/00004836-199810000-00009.
22. Glasgow RE, Cho M, Hutter MM, et al. The spectrum and cost of complicated gallstone disease in California. Arch Surg 2000;135:1021–1025. doi:10.1001/archsurg.135.9.1021.

GN98 Clarification Regarding Meniscal Injuries

Question: Should GN98 SIGNIFICANT INJURIES TO LIGAMENTS AND TENDONS be modified to include injuries to the meniscus?

Question source: HERC staff; provider

Issue: Multiple joint injury ICD-10 codes are included on both or one of two covered lines (line 381 DISRUPTIONS OF THE LIGAMENTS AND TENDONS OF THE ARMS AND LEGS, EXCLUDING THE KNEE, RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT or line 436 INTERNAL DERANGEMENT OF KNEE AND LIGAMENTOUS DISRUPTIONS OF THE KNEE, RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT) and on an uncovered line (line 611 SPRAINS AND STRAINS OF ADJACENT MUSCLES AND JOINTS, MINOR); code placement is determined by GN98 SIGNIFICANT INJURIES TO LIGAMENTS AND TENDONS. Only significant injuries are intended for inclusion on line 381/436. Currently, GN98 only includes reference to injuries to tendons and ligaments. However, the ICD-10 codes for meniscal injury and derangement are also included on both covered and uncovered lines.

The current GN98 replaces the previous delineation of these lines, which was based on line titles limiting inclusion on the upper line to "grade 2 and 3" injuries. The Sports Medicine experts, as well as the orthopedic experts, felt that this grading system applied to only one type of injury on these lines (acromioclavicular joint sprain). They recommended a name change for these lines to better represent the HERC intent to have more severe injuries only included on the upper, covered, lines. They also recommended a new guideline to also clarify intent. The intent of the guideline note as written by the ICD-10 Sports Medicine/Orthopedic reviewers was to allow significant injuries to be covered on the upper line while non-significant injuries were not covered and included only on the lower line. Meniscal injuries were not considered in these discussions.

Injuries to menisci can occur with trauma, or with degenerative changes. Typical symptoms of torn or deranged menisci include knee pain, joint swelling, joint locking (the inability to extend the knee fully), or a sensation that the knee is going to give way. Conservative treatment of meniscal injuries include physical therapy, anti-inflammatories, and corticosteroid injections.

Evidence supports only conservative therapy for degenerative meniscal injuries. Traumatic meniscal injuries which also involve ligament injury are candidates for surgical repair.

Currently, GN98 limits all treatment of non-significant injuries to ligaments and tendons to the uncovered line 611. Some of these injuries might also benefit from PT, or other conservative therapy.

HERC staff recommendation:

1) Modify GN98 as shown below
    a. Include meniscal injury (blue wording)
    b. Meniscal injuries that result in interference with motion or which accompany significant ligament instability should have surgical correction
    c. Consider whether non-significant injuries should have coverage of conservative therapy such as PT. Is yes, then the guideline will need to be further revised.

GUIDELINE NOTE 98, SIGNIFICANT INJURIES TO LIGAMENTS AND TENDONS AND MENISCI

Lines 381,436,611

Significant injuries to ligaments and/or tendons and/or menisci are those that result in clinically demonstrable joint instability or mechanical interference with motion. Significant injuries are covered on Line 381 or Line 436; non-significant injuries are included on Line 611.

Tympanostomy Tubes and Adenoidectomy for Chronic Otitis Media with Hearing Loss

Questions:

1) Should adenoidectomy CPT codes be added to the hearing loss lines?
2) Should the chronic otitis media with effusion (COME) that results in hearing loss be paired with tympanostomy tube placement and adenoidectomy for children over age 5 with other special risk factors such as craniofacial anomalies or speech/language delay?
    a. Should COME with hearing loss in normal children be prioritized to a higher line?
3) Should adenoidectomy be covered with the first tube placement procedure?

Question source: HERC staff, HSD staff, ENT providers

Issues:

1) Guideline Note 51 regarding coverage of treatments for chronic otitis media mentions adenoidectomy with second placement of tympanostomy tubes; however, the CPT codes for adenoidectomy do not appear on line 316 HEARING LOSS - AGE 5 OR UNDER which is one of the lines mentioned in the guideline. The appropriate codes do appear on line 479 CHRONIC OTITIS MEDIA; OPEN WOUND OF EAR DRUM, which is below the current funding line.
2) Providers and CCO medical directors are requesting clarification of HERC intent regarding coverage for PE tubes for children over age 5 with hearing loss and COM and other special risk factors. GN51 discusses coverage for tympanostomy tubes for hearing loss without specifying the age of the child. Line 316 HEARING LOSS - AGE 5 OR UNDER is mentioned in the GN, but line 450 HEARING LOSS - OVER AGE OF FIVE is not. Additionally, Line 450 does not have CPT codes for tympanostomy tube placement or for adenoidectomy. Review of the 2012-2013 discussion regarding this guideline and accompanying code/line changes does not find any discussion of limiting the benefit by age. The current guideline and lines appears to imply that the HERC intended that children older than age 5 with chronic otitis media and hearing loss with other risk factors should not be covered for tympanostomy tube placement and/or adenoidectomy.
    a. ENT providers are requesting that children with COME and prolonged hearing loss without other special risk factors be considered for coverage for tympanostomy tubes and adenoidectomy. The HERC has previously addressed this question on several occasions, and concluded that only children with language delay and hearing loss, craniofacial anomalies, or other high risk factors with COME were intended for inclusion on the covered line (316). Children without high risk factors were included on line 479, which is unfunded. The lower placement was due to the fact that tympanostomy tubes provide only a short-term benefit, and have no proven long term effect on language or speech. The lack of funding for line 479 is due to the movement of the funding line by the Legislature a few years ago; previously this line was among the last funded lines on the Prioritized List.
3) On staff review of this issue, new literature was identified that provided evidence of benefit of adenoidectomy with the first PE tube placement. Currently, adenoidectomy is an option with the second PE tube placement procedure.

HERC history

Chronic otitis media in children was reviewed in a 2012 coverage guidance which was reaffirmed in 2014. A rescan was recently completed for this coverage guidance, which found:

> In general, the literature supports the 2014 findings that interventions for chronic otitis media result in short-term improvements in hearing and resolution of the effusion, but that long-term differences are negligible or non-existent. Since 2014, there is new evidence that adenoidectomy, with or without other interventions, may also improve short-term outcomes particularly in children over the age of 4 years (Boonacker et al., 2014; Mikals & Brigger, 2014; Rosenfeld et al., 2016; Wallace et al., 2014). There is also a recent Cochrane review that found that antibiotics were effective for resolution of effusion at 2-3 months, but with higher rates of diarrhea, vomiting, and skin rash (Venekamp et al., 2016).

Based on this rescan, EGBS did not feel that a review of the 2014 coverage guidance was required.

BAHA hearing aids are included on line 450 HEARING LOSS OVER THE AGE OF 5 for children with severe to profound hearing loss in one ear. The vast majority of children with COME would not have severe or profound hearing loss (i.e. deaf) in one ear with normal hearing in the other. Therefore, BAHA would not be a normal treatment for COME.

From Dr. Kristi Seidel, Family Practice physician in Eugene and Medical Director at Trillium Community Health Plan

> The issue of concern is the lack of coverage for PE tubes and adenoidectomy for children over the age of 5 with conductive hearing loss due to chronic otitis media with effusion. The ENT providers state that current standard of care is to follow the child with watchful waiting for 6 months and if there is no improvement or if the hearing loss worsens, PE tubes should be placed. If the tubes become extruded (common with growth) and the condition has not resolved, PE tubes are typically placed a second time and at that time it is standard of care, in patients who are at least 3 years of age, to remove the adenoids when placing the second set of PE tubes.
>
> Conductive hearing loss in a child > 5 years old is found on line 450, funded, however, it does not include PE tubes or adenoidectomy in the covered procedures for this line. It does include implantation of a BAHA device (69717, 69718) if the condition is unilateral.
>
> Several ENTs have voiced concern that they can only treat unilateral conductive hearing loss (it is often bilateral in these children) and the covered treatment is limited to the very invasive, expensive treatment of a BAHA (Bone Anchored Hearing Aid) device. They feel implantation of a BAHA is too aggressive for this diagnosis, but they feel this is the only option OHP will allow for these kids. If the member has chronic OM with effusion and their hearing is normal or minimally affected, they are very comfortable continuing to follow conservatively. But when the hearing loss is >25-30dB in both ears, for over 6-12 months they really would like to provide the PE tubes for the members. (Our claims review shows we spend approximately $1100 for a set of tubes, and about $11,700 for a BAHA.)

Current List guidelines

GUIDELINE NOTE 51, CHRONIC OTITIS MEDIA WITH EFFUSION

Lines 316,479

Antibiotic and other medication therapy (including antihistamines, decongestants, and nasal steroids) are not indicated for children with chronic otitis media with effusion (OME) (without another appropriate diagnosis).

Patients with specific higher risk conditions (including craniofacial anomalies, Down's syndrome, and cleft palate, or documented speech and language delay) along with hearing loss and chronic otitis media with effusion are intended to be included on Line 316. Otherwise hearing loss associated with chronic otitis media with effusion (without those specific higher risk conditions) is only included on Line 479.

For coverage to be considered on either Line 316 or Line 479, there should be a 3 to 6 month watchful waiting period after diagnosis of otitis media with effusion, and if documented hearing loss is greater than or equal to 25dB in the better hearing ear, tympanostomy surgery may be indicated, given short- but not long-term improvement in hearing. Formal audiometry is indicated for children with chronic OME present for 3 months or longer. Children with language delay, learning problems, or significant hearing loss should have hearing testing upon diagnosis. Children with chronic OME who are not at risk for language delay (such as those with hearing loss <25dB in the better hearing ear) or developmental delay should be reexamined at 3- to 6-month intervals until the effusion is no longer present, significant hearing loss is identified, or structural abnormalities of the eardrum or middle ear are suspected.

Adenoidectomy is not indicated at the time of first pressure equalization tube insertion. It may be indicated in children over 3 years who are having their second set of tubes.

Removal of retained tympanostomy tubes requiring anesthesia (CPT code 69424) or as an office visit, is included on Line 428 as a complication, pairing with ICD-10-CM H74.8.

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

GUIDELINE NOTE 103, BONE ANCHORED HEARING AIDS

Lines 316,450

Bone anchored hearing aids (BAHA, CPT 69714, 69715) are included on these lines when the following criteria are met:

A) The patient is aged 5-20 years for implanted bone anchored hearing aids; headband mounted BAHA devices may be used for children under age 5
B) Treatment is for unilateral severe to profound hearing loss when the contralateral ear has normal hearing with or without a hearing aid
C) Traditional air amplification hearing aids and contralateral routing of signal (CROS) hearing aid systems are not indicated or have been tried and are found to be not effective
D) Implantation is unilateral.

Use of BAHA for treatment of tinnitus is not covered

Evidence

1) **Washington HTA 2015**, systematic review of tympanostomy tubes Study not included in packet due to length.
    a. Studies on improvement in hearing included children up through age 7
    b. Studies on speech and language development included children up to age 4.7 yrs
    c. Short term improvement in hearing; no long term difference with watchful waiting. No difference in behavioral scores or educational outcomes/scores with tympanostomy tubes vs watchful waiting.
2) **Boonacker 2014**, (Report not included in packet due to length, see online version: https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0083658/pdf/PubMedHealth_PMH0083658.pdf) systematic review of adenoidectomy with or without tympanostomy tubes ("grommets") for COME
    a. N= 10 studies, including 1761 children
        i. 8 at low risk of bias, 2 at moderate risk
    b. Indication for surgery included recurrent acute otitis media or COME
    c. "Failure" of treatment defined as one or more of the following:
        i. four or more AOM episodes (including episodes of otorrhea) per year
        ii. presence of effusion for ≥ 50% of the time (i.e. effusion for > 6 months)
        iii. need for additional surgery
        iv. hearing improved by < 10 dB.
    d. Children (N=343) randomized to non-surgical treatment: 193 (56%) had failure to improve at 12 months
        i. The absolute risk of failing to improve for children with an indication of persistent OME was 89%
    e. The proportion of children who failed at 12 months in the adenoidectomy group (adenoidectomy with or without grommets) was 32% whereas the proportion of children who failed at 12 months in the no adenoidectomy (non-surgical or grommets alone) group was 45%. The unadjusted for failure at 12 months was –13% [95% confidence interval (CI) –17% to –8%], resulting in a number needed to treat (NNT) of eight children to prevent one failure. The adjusted RR was 0.76 (95% CI 0.69 to 0.85), which was similar to the unadjusted RR (0.72, 95% CI 0.63 to 0.81). For all secondary outcomes, with the exception of presence of effusion for ≥ 50% of the time in the first 12 months, results for children in the adenoidectomy group were also statistically significantly better than results for those in the no adenoidectomy group.
    f. The effects in the secondary comparisons also showed that children who have had their adenoid removed have a greater chance of clinical improvement. The size of that effect is, in general, small but persists for at least 2 years after surgery. Two subgroups of children are most likely to benefit from adenoidectomy. These are (1) children with recurrent AOM aged < 2 years and (2) children aged ≥ 4 years with persistent OME. The proportion of children aged < 2 years with recurrent AOM who failed at 12 months was 16% (44/281) in the adenoidectomy group and 27% (120/438) in the group who did not have adenoidectomy (RD 12%, 95% CI 6% to 18%; NNT = 8; adjusted RR 0.63, 95% CI 0.47 to 0.85). In contrast, in children aged ≥ 2 years with recurrent AOM, no benefit of adenoidectomy was seen; 18% (8/44) of the children in the adenoidectomy group failed at 12 months and 3% (1/40) of the group who did not have adenoidectomy failed (RD 16%, 95% CI 3% to 28%, in favour of no adenoidectomy; adjusted RR 4.96, 95% CI 0.69 to 35.5). The proportion of children aged ≥ 4 years with persistent OME who failed at 12

months was 51% (163/322) in the adenoidectomy group and 70% (289/415) in the group who did not have adenoidectomy (RD 19%, 95% CI 12% to 26%; NNT = 6; adjusted RR 0.77, 95% CI 0.68 to 0.86). In contrast, in children aged < 4 years with persistent OME, no significant benefit of adenoidectomy was seen; 23% (30/128) of the children in the adenoidectomy group failed at 12 months and 30% (33/111) of the group who did not have adenoidectomy failed (RD 7%, 95% CI –5% to 18%; adjusted RR 0.98, 95% CI 0.69 to 1.38).

g. Conclusion: Children with OM who have their adenoid removed have a greater chance of clinical improvement: eight children need to receive adenoidectomy to prevent one failure. Adenoidectomy is most beneficial in children aged ≥ 4 years with persistent OME (six children needing adenoidectomy to prevent one failure). A smaller beneficial effect was found in children with recurrent AOM aged < 2 years (nine children needing adenoidectomy to prevent one failure). No beneficial effect was seen in children aged < 4 years with persistent OME or in those aged ≥ 2 years with recurrent AOM.

3) **Merkels 2014 (Document not included in packet due to length; see online version: http://jamanetwork.com/journals/jamaotolaryngology/fullarticle/1782135)** , systematic review and meta-analysis of adenoidectomy as adjuvant treatment with tympanostomy tubes (TT)
   a. N=15 studies examining the risk of repeat TT tube placement (r-TT)
   b. Ten studies (n = 71 353) reported that primary adenoidectomy + TT decreased the risk of r-TT or risk of recurrent acute otitis media (RAOM), OME, or otorrhea compared with TT alone.
   c. Four studies (n = 538) reported no difference between Ad + TT groups compared with TT-only groups in the prevention of r-TT or of RAOM, OME, or otorrhea.
   d. limited meta-analysis and pooling of data revealed that the estimated rate of r-TT for children undergoing primary adenoidectomy was 17.2%(95%CI, 12.2%-22.2%) vs 31.8%(95%CI, 23.9%-39.8%) for children undergoing primary TT only. When stratified by age younger than 4 years, the protective effects of adenoidectomy were diminished.
   e. CONCLUSIONS The current evidence suggests that primary adenoidectomy + TT may be superior to TT only in decreasing the risk of r-TT and the risk of RAOM, OME, or otorrhea.

4) **Wallace 2014 (Document not included in packet due to length; see online version: http://pediatrics.aappublications.org/content/pediatrics/early/2014/01/01/peds.2013-3228.full.pdf)**, systematic review of surgical treatments for OME
   a. N=41 studies
   b. In comparison with watchful waiting or myringotomy (or both), tubes decreased time with OME and improved hearing; no specific tube type was superior.
   c. Adenoidectomy alone, as an adjunct to myringotomy, or combined with tubes, reduced OME and improved hearing in comparison with either myringotomy or watchful waiting.
      i. No comparison was done of tubes with adenoidectomy vs tubes alone
   d. Tubes and watchful waiting did not differ in language, cognitive, or academic outcomes.
   e. Otorrhea and tympanosclerosis were more common in ears with tubes. Adenoidectomy increased the risk of postsurgical hemorrhage.
   f. CONCLUSIONS: Tubes and adenoidectomy reduce time with OME and improve hearing in the short-term. Both treatments have associated harms.

Expert guidelines

1) **Rosenfeld 2016**, **(Document not included in packet due to length; see online version:** http://journals.sagepub.com/doi/pdf/10.1177/0194599815624407) AAOM practice guideline for OME
   a) Strong recommendation against antibiotics for OME
   b) New recommendation: Clinicians should recommend tympanostomy tubes when surgery is performed for OME in a *child less than 4 years old*; adenoidectomy should not be performed unless a distinct indication (eg, nasal obstruction, chronic adenoiditis) exists other than OME. (Grade B, moderate strength of evidence)
   c) Recommendation: Clinicians should recommend tympanostomy tubes, adenoidectomy, or both when surgery is performed for OME in a *child 4 years old or older.* This should be shared decision making.
   d) Adenoidectomy may be contraindicated in children with cleft palate or syndromes associated with a risk of velopharyngeal insufficiency

HERC staff summary:
The benefit of tympanostomy tubes +/- adenoidectomy for COME remains limited, with short-term benefits for hearing but no long-term benefits for hearing, speech or language development, or school/behavioral outcomes. There is a growing body of evidence that indicates that adenoidectomy may be beneficial with the first set of PE tube placement; however, expert guidelines do not recommend adenoidectomy at all for children under age 4, and shared decision making for children aged 4 and older.

HERC staff recommendations:

1) Do not expand coverage to children of any age with COME with hearing loss without other high risk conditions
    a. Limited evidence of any long-term benefit
    b. Significant fiscal impact
2) Add adenoidectomy CPT codes to lines 316 HEARING LOSS - AGE 5 OR UNDER
    a. CPT 42830 Adenoidectomy, primary; younger than age 12
    b. CPT 42835 Adenoidectomy, secondary; younger than age 12
    c. Utilization is covered by GN51 and would be limited to children with special risk factors aged 4 and older for second set of PE tubes only
    d. The CPT codes for adenoidectomy for children age 12 and older are not appropriate as the line is specific for children aged 5 and under
3) Add treatment for chronic otitis media resulting in hearing loss for children with high risk conditions older than age 5
    a. Add tympanostomy tube placement codes to line 450
        i. CPT 69433 Tympanostomy (requiring insertion of ventilating tube), local or topical anesthesia
        ii. CPT 69436 Tympanostomy (requiring insertion of ventilating tube), general anesthesia
    b. Add adenoidectomy codes to line 450 for young children
        i. CPT 42830 Adenoidectomy, primary; younger than age 12
        ii. CPT 42835 Adenoidectomy, secondary; younger than age 12
    c. Consider adding adenoidectomy codes for older children
        i. CPT 42831 Adenoidectomy, primary; age 12 or over
        ii. CPT 42836 Adenoidectomy, secondary; age 12 or over
        iii. Children aged 12 and over should no longer be at risk for speech/language delay
    d. Add line 450 HEARING LOSS - OVER AGE OF FIVE to GN51 CHRONIC OTITIS MEDIA WITH EFFUSION
        i. See edits below

GUIDELINE NOTE 51, CHRONIC OTITIS MEDIA WITH EFFUSION

Lines 316,450,479

Antibiotic and other medication therapy (including antihistamines, decongestants, and nasal steroids) are not indicated for children with chronic otitis media with effusion (OME) (without another appropriate diagnosis).

Patients with specific higher risk conditions (including craniofacial anomalies, Down's syndrome, and cleft palate, or documented speech and language delay) along with hearing loss and chronic otitis media with effusion are intended to be included on Line 316 or line 450. Otherwise hearing loss associated with chronic otitis media with effusion (without those specific higher risk conditions) is only included on Line 479.

For coverage to be considered on either Line 316, Line 450 or Line 479, there should be a 3 to 6 month watchful waiting period after diagnosis of otitis media with effusion, and if documented hearing loss is greater than or equal to 25dB in the better hearing ear, tympanostomy surgery may be indicated, given short- but not long- term improvement in hearing. Formal audiometry is indicated for children with chronic OME present for 3 months or longer. Children with language delay, learning problems, or significant hearing loss should have hearing testing upon diagnosis. Children with chronic OME who are

not at risk for language delay (such as those with hearing loss <25dB in the better hearing ear) or developmental delay ~~(~~should be reexamined at 3- to 6-month intervals until the effusion is no longer present, significant hearing loss is identified, or structural abnormalities of the eardrum or middle ear are suspected.

Adenoidectomy is not indicated at the time of first pressure equalization tube insertion. It may be indicated in children over 3 years who are having their second set of tubes.

Section 8.0

Previously Discussed Items

Preventive services USPSTF edits

Question: Should Guideline Note 106 for preventive services be modified for clarity?

Question source: HERC Staff

Issue: In October 2016 the guideline note on preventive services was edited to include language about federal law. It is possible that federal laws may change about what is required by insurers (i.e. through repeal of the ACA). For clarity, this guideline can be changed to avoid confusion about HERC intent about coverage of preventive services, should federal law change. This guideline will need to be updated in conjunction with each January 1st list to include the additional years' worth of recommendation that will be going into effect (those recommendations approved during the calendar year two years prior).

Also, the USPSTF "D" recommendations now fall on an unfunded line. However, even if there were funding to expand coverage to this area of the Prioritized List, these are still not recommended services. Therefore the staff recommendation is to remove them from the List altogether (including an unfunded line) to signify the intent for noncoverage of services that are not recommended.

Recommendations:

GUIDELINE NOTE 106, PREVENTIVE SERVICES

Line 3

Included on this line are the following preventive services: ~~as required by federal law:~~

1. US Preventive Services Task Force (USPSTF) "A" and "B" Recommendations in effect and issued prior to January 1, 2016:
   http://www.uspreventiveservicestaskforce.org/Page/Name/uspstf-a-and-b-recommendations/
   a. USPSTF "D" recommendations are not included on this line or any other line of the Prioritized List
2. American Academy of Pediatrics (AAP) Bright Futures Guidelines:
   http://brightfutures.aap.org. Periodicity schedule available at http://www.aap.org/en-us/professional-resources/practice-support/Periodicity/Periodicity%20Schedule_FINAL.pdf.
3. Health Resources and Services Administration (HRSA) Women's Preventive Services - Required Health Plan Coverage Guidelines:
   As retrieved from http://www.hrsa.gov/womensguidelines/ on 1/1/2017.
4. Immunizations as recommended by the Advisory Committee on Immunization Practices (ACIP):
   http://www.cdc.gov/vaccines/schedules/hcp/index.html

~~USPSTF "D" recommendations are included on line 625, PREVENTION SERVICES WITH LIMITED OR NO EVIDENCE OF EFFECTIVENESS.~~

Bariatric Surgery and Marijuana Use

Question: Should current marijuana use be a contraindication for bariatric surgery?

Question source: VBBS

Issue: The bariatric surgery guideline was recently updated at the October, 2016 VBBS/HERC meetings. The major topic of that discussion was regarding tobacco cessation. Marijuana use had previously been an exclusion to surgery—patients must be "abstinent from illicit drugs." However, marijuana is now legal in Oregon for both medical and recreational use. The Obesity Task Force had specifically examined the question about use of marijuana prior to bariatric procedures.

The summary of the VBBS discussion is below:

> Livingston discussed one of the recommendations by the Obesity Task Force with regard to a 6-month absence of abuse or dependence of marijuana needed prior to the procedure. Members raised that despite the legality of marijuana, there are clear clinical implications of increasing appetite. Marijuana was confirmed to be used to treat cachexia (wasting syndrome). Dr. Bruce Wolfe, the appointed expert on this topic, introduced himself. Wolfe stated the evidence is unknown whether the weight loss goals of bariatric surgery may be compromised by the use of marijuana. He said surgeons do not want to perform surgery on people who have an active addiction. Twenty percent of bariatric surgery candidates are active smokers and may quit for surgery, but by 2-3 years later many are smoking again. Smoking marijuana may affect postoperative complications.

Based on the discussion above, a clause was added to maKe abuse or dependence of marijuana in the 6 month pre-operative period a contraindication to surgery. However, there was no mention about casual marijuana use. The relevant changes to the guideline is excerpted below.

> D) 1) b) Must remain free of abuse of or dependence on alcohol or marijuana 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 illicit drugs. Tobacco abstinence to be confirmed in active smokers by negative cotinine levels at least 6 months apart, with the second test within 1 month of the surgery date.

VBBS staff was asked to review the evidence of the impact of marijuana use on bariatric surgery outcomes, including post-operative complications and lack of effectiveness for weight loss. The major concern of VBBS was that marijuana was useful for weight gain for certain conditions (i.e. AIDS, cachexia). Staff undertook a review of the evidence for the effectiveness of marijuana on weight gain for medication conditions such as cachexia, as well as evidence of harms of marijuana use related to bariatric surgery.

Evidence for marijuana use for treatment of cachexia

1) **Lutge 2013**, cannabis in HIV/AIDS (document found here: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005175.pub3/epdf)
    a. N=7 studies, all RCTs
        i. Considerable issue with blinding given the psychoactive effects
    b. The evidence for substantial effects on morbidity and mortality is currently limited. Data from only one relatively small study (n=139, of which only 88 were evaluable), conducted in the period before access to highly-active antiretroviral therapy (HAART), showed that patients administered dronabinol were twice as likely to gain 2kg or more in body weight (RR 2.09), but the confidence interval for this measure (95% CI 0.72 - 6.06) included unity. The mean weight gain in the dronabinol group was only 0.1kg, compared with a loss of 0.4kg in the placebo group.
    c. **Authors' conclusions:** Despite dronabinol being registered by at least some medicines regulatory authorities for the treatment of AIDS-associated anorexia, and some jurisdictions making allowances for the "medical" use of marijuana by patients with HIV/AIDS, evidence for the efficacy and safety of cannabis and cannabinoids in this setting is lacking. The studies to date have been of short duration, in small numbers of patients, and have focused on short-term measures of efficacy. Long-term data, showing a sustained effect on AIDS related morbidity and mortality and safety in patients on effective antiretroviral therapy, has yet to be presented.
2) **Belendiuk 2015 (Not included in packet due to length; view online):** , review of effects of marijuana on commonly approved medical indications
    a. Marijuna use for cachexia from HIV/AIDS or cancer:
        i. …studies demonstrate that marijuana has positive effects on cachexia resulting from a medical condition, but are largely limited by small sample sizes. Additionally, studies comparing THC to FDA-approved medication (i.e., megestrol) indicate that THC is less effective in promoting appetite and weight gain.
        ii. In sum, there is moderate support for the use of cannabinoids for cachexia/wasting. Additional studies with larger sample sizes that examine the efficacy of marijuana compared to nutritional support/calorie augmentation in the treatment of cachexia are indicated.
3) **Strasser 2006**, **(Not included in packet due to length;** view online) RCT for cannabis vs placebo for cancer related anorexia-cachexia
    a. N=243 (95 cannabis extract, 100 THC, 48 control)
    b. Intent-to-treat analysis showed no significant differences between the three arms for appetite, QOL, or cannabinoid-related toxicity. Increased appetite was reported by 73%, 58%, and 69% of patients receiving CE, THC, or PL, respectively. An independent data review board recommended termination of recruitment because of insufficient differences between study arms.
    c. Conclusion: No differences in patients' appetite or QOL were found either between CE, THC, and PL or between CE and THC at the dosages investigated.

Evidence for marijuana on bariatric surgery:

1) **Rummel 2014**, review of marijuana use and bariatric surgery
    a. Reviewed the known risk of complications from alcohol and tobacco use perioperatively
    b. No empirical research to date has examined the effects of cannabis use after weight loss surgery.

c. Effects of cannabis on surgical complications:
    i. There is no isolated data regarding surgical outcomes for historical cannabis abusers.
    ii. In a few studies, patients who successfully completed substance abuse treatment actually had higher post-operative weight loss than patients with no substance abuse diagnoses.
    iii. There may be a hypothesized potential for cannabis use to exacerbate post-surgical complications; however, this remains undocumented in the medical literature.
d. Overall impact on health:
    i. It is clear that long-term, regular marijuana use has many negative effects. However, there is little research to support negative effects of short-term or irregular use.
e. Effect of cannabis on weight:
    i. Interestingly, in one sample of female weight management patients, lower rates of past year marijuana use were actually associated with higher BMI.
    ii. Current research has actually demonstrated a lower prevalence of obesity in cannabis users as compared to non-users.
    iii. There is a lack of empirical evidence to suggest a link between cannabis use and chronic overeating.
f. Recommendations:
    i. For patients who do report irregular recreational marijuana use, or more recent problematic use, the employment of informed consent documents may be helpful
    ii. For patients who have a history of non- adherence, the use of a behavioral contract may be helpful. A behavioral contract "spells out in clear terms the behavioral expectations of the team, and patients sign their agreement to those recommendations."
    iii. Patients assessed to be at increased risk for substance abuse or dependence may be required to attend a planned treatment intervention

2) **Vidot 2016**, (Not included in packet; view online) post operative marijuana use in bariatric surgery
    a. N=50, retrospective cohort study
    b. A loss of controlled food intake was associated with current (P = .02) and increased post-WLS use (P = .01). Increased use and/or regular marijuana use predicted higher scores on eating disorder subscales compared with respective counterparts (P < .05). Current use did not significantly predict higher scores on the Yale Food Addiction Scale.
    c. Unclear from presented data if there was any difference in post-operative BMI change among marijuana users compared to non-users
        i. Rummell's comments on the Vidot study: In terms of weight loss outcomes, a brief examination of patient BMI in Vidot et. al.'s sample reveals that patients who reported marijuana use within the 30 days to 1 year had the highest postsurgical BMI (39.6 and 37.0, respectively). Patients who had never used marijuana had an average BMI similar to that of the overall sample (35.3). Interestingly, patients who reported *increased* marijuana use since surgery had the *lowest* average postoperative BMI (30.4), also with the least amount of variation. This is reminiscent of previous research demonstrating lower rates of obesity in cannabis users compared with nonusers.

d. Conclusions: Findings indicated marijuana use in post-WLS patients despite recommendations against use. A subgroup of WLS patients may be at risk for disordered eating post-WLS, particularly those who used marijuana before surgery, and should be closely monitored for several years post-WLS.

HERC staff summary:
The efficacy of marijuana for treatment of anorexia/cachexia related to cancer and HIV/AIDS appears to be mixed, and any positive effect appears to be small.

The following evidence was found regarding marijuana use and bariatric surgery outcomes:

- post-operative infections: little to no evidence that this is a concern (Vidot et al, 2016)
- post-operative weight gain: unclear evidence (Lutge et al, 2013) (Vidot et al 2014)
- post-operative loss of food control: weak evidence that marijuana users have more loss of food control after bariatric surgery than non-marijuana users (Vidot et al, 2016)
- post-operative complications: rare case studies demonstrating ACS with marijuana use (Casier et al, 2014), weak evidence to risk of infection, immunosuppression (Vidot et al, 2014), moderate evidence for risk of hyperemesis and chronic bronchitis (Vidot et al, 2014)
- There is an unclear relationship between marijuana use and BMI, and the data currently indicates that marijuana users have a lower BMI than non-marijuana users.

Based on the evidence above, there is no clear, compelling, consistent evidence that marijuana use would jeopardize the success of bariatric surgery or result in significant post-operative weight gain.

HERC staff recommendation:

1) Make no changes to GN8 BARIATRIC SURGERY
    a. Continue to exclude marijuana abuse or dependence prior to bariatric surgery but allow casual use until more evidence is published about the effects of marijuana use on the outcomes of bariatric surgery
    b. Consistent with major expert recommendations

GUIDELINE NOTE 8, BARIATRIC SURGERY

Line-325

Bariatric/metabolic surgery (limited to Roux-en-Y gastric bypass~~,~~ and sleeve gastrectomy) is included on Line 325 when the following criteria are met:

A) Age ≥ 18
B) The patient has obesity with a:
    1) BMI ≥ 40 OR
    2) BMI ≥ 35 with:
        a) Type 2 diabetes, OR
        b) at least two of the following other serious obesity-related comorbidities: hypertension, coronary heart disease, mechanical arthropathy in major weight bearing joint, sleep apnea
C) Repeat bariatric surgery is included when it is a conversion from a less intensive (such as gastric band or sleeve gastrectomy) to a more intensive surgery (e.g. Roux-en-Y). Repair of surgical complications (excluding failure to lose sufficient weight) are also included on this and other lines. Reversal of surgical procedures and devices is included on this line when benefits of reversal outweigh harms.

D) Participate in the following four evaluations and meet criteria as described.
   1) Psychosocial evaluation: (Conducted by a licensed mental health professional)
      a) Evaluation to assess potential compliance with post-operative requirements.
      b) Must remain free of abuse of or dependence on alcohol or marijuana 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 quit date and within 1 month of the surgery to confirm abstinence from illicit drugs. Tobacco abstinence to be confirmed in active smokers by negative cotinine levels at least 6 months apart, with the second test within 1 month of the surgery date.
      c) No mental or behavioral disorder that may interfere with postoperative outcomes[1].
      d) Patient with psychiatric illness must be stable for at least 6 months.
   2) Medical evaluation: (Conducted by OHP primary care provider)
      a) Pre-operative physical condition and mortality risk assessed with patient found to be an appropriate candidate.
      b) Optimize medical control of diabetes, hypertension, or other co-morbid conditions.
      c) Female patient not currently pregnant with no plans for pregnancy for at least 2 years post-surgery. Contraception methods reviewed with patient agreement to use effective contraception through 2nd year post-surgery.
   3) Surgical evaluation: (Conducted by a licensed bariatric surgeon associated with program[2])
      a) Patient found to be an appropriate candidate for surgery at initial evaluation and throughout period leading to surgery.
      b) Received counseling by a credentialed expert on the team regarding the risks and benefits of the procedure~~3~~ and understands the many potential complications of the surgery (including death) and the realistic expectations of post-surgical outcomes.
   4) Dietician evaluation: (Conducted by licensed dietician)
      a) Evaluation of adequacy of prior dietary efforts to lose weight. If no or inadequate prior dietary effort to lose weight, must undergo six-month clinically supervised weight reduction program (including intensive nutrition and physical activity counseling as defined by the USPSTF).
      b) Counseling in dietary lifestyle changes

E) Participate in additional evaluations:
   1) Post-surgical attention to lifestyle, an exercise program and dietary changes and understands the need for post-surgical follow-up with all applicable professionals (e.g. nutritionist, psychologist/psychiatrist, exercise physiologist or physical therapist, support group participation, regularly scheduled physician follow-up visits).

[1] Many patients (>50%) have depression as a co-morbid diagnosis that, if treated, would not preclude their participation in the bariatric surgery program.

[2] All surgical services must be provided by a program with current accreditation (as a comprehensive center or low acuity center) by the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP).

OBES SURG (2014) 24:1764–1770
DOI 10.1007/s11695-014-1315-x

REVIEW ARTICLE

Assessing Marijuana Use in Bariatric Surgery Candidates: Should It Be a Contraindication?

Christina M. Rummell · Leslie J. Heinberg

Published online: 7 June 2014

Abstract Research has demonstrated negative effects of both alcohol and tobacco use after bariatric surgery. However, no research to date has examined effects of cannabis use after bariatric surgery, even though cannabis is the most commonly used illicit drug in the USA. Literature review reveals that many practitioners generalize from data regarding alcohol abuse to all substances. Further, many screening protocols fail to differentiate between varying levels of cannabis use. The current report aims to (1) review the relevant literature on marijuana use and its potential consequences among bariatric patients, (2) discuss relevant problems and gaps in this literature, and (3) make preliminary recommendations regarding the assessment and treatment planning of bariatric candidates who disclose marijuana use.

Keywords Bariatric surgery · Weight loss surgery · Cannabis · Marijuana · Substance use disorder · Illicit drug use · Recommendations

Introduction: Criteria for Weight Loss Surgery Candidate Selection

Substance abuse as a contraindication for weight loss surgery was first noted by the National Institute of Health (NIH) in their (1991) *Consensus Statement* [1] and has continued as a contraindication in published guidelines [2]. This prohibition may be because negative post-operative health complications are hypothesized to result from abuse of substances both pre- and post-operatively or because of the belief that such use portends other domains of non-adherence.

Regarding specific substances, clinical guidelines have discussed the clear negative effects of both alcohol and nicotine use after surgery [2-4]. For example, alcohol use can lead to weight regain, liver damage, dehydration, malnutrition, and ulcers after surgery [5]. Post-surgically, patients are significantly more sensitive to the effects of alcohol [6, 7], and more recent work suggests an increased risk of alcohol use disorders following surgery—particularly Roux-en-Y gastric bypass (RYGB) [8, 9]. In the American Association of Clinical Endocrinologists/The Obesity Society/American Society for Metabolic and Bariatric Surgery (AACE/TOS/ASMBS) 2013 clinical practice guidelines for bariatric surgery, it is recommended that patients eliminate all alcohol consumption post-surgically [2].

In a similar vein, tobacco use increases the risk of death associated with bariatric surgery and increases the risk of developing post-surgical complications such as marginal ulcers and infection, and tobacco users tend to require more pain management after surgery [10]. The AACE/TOS/ASMBS guidelines suggest abstinence from tobacco products for 6 weeks prior to surgery, though some report that an even shorter time period is also acceptable [2].

Regarding the effects of other illicit drugs on surgical outcomes, there is some evidence that cocaine use can cause vasculitis leading to both ischemic and hemorrhagic strokes [11]. There is one published case study of an 18-year-old female RYGB patient who had used cocaine pre- and post-surgery and evidenced a stroke 4 months post-surgery. However, no definitive evidence was found upon medical examination to link the cause of the stroke to drug use [12]. The effects of other substances are largely undescribed.

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