



**Health Evidence Review
Commission's
Value-based Benefits Subcommittee**

October 10, 2013

**Meridian Park Hospital
Community Health Education Center, Room 117B&C
19300 SW 65th Avenue, Tualatin, OR 97062**

Section 1.0

Call to Order

AGENDA
VALUE-BASED BENEFITS SUBCOMMITTEE
October 10, 2013
9:00am - 1:00pm
Meridian Park Hospital
Community Health Education Center, Room 117B&C
19300 SW 65th Avenue, Tualatin, OR 97062
A working lunch will be served at approximately 12:00 PM
All times are approximate

I.	Call to Order, Roll Call, Approval of Minutes – Lisa Dodson	8:30 AM
II.	Staff report –Ariel Smits, Cat Livingston, Darren Coffman	8:35 AM
III.	Consent Agenda/Straight Forward Items – Ariel Smits A. Straightforward table B. Straightforward changes to guidelines and coding specifications	8:45 AM
IV.	2014 CPT code review – Ariel Smits	9:00 AM
V.	Biennial Review – Ariel Smits A. Fibromyalgia B. Open wound of eardrum	10:30 AM
VI.	Coverage Guidances for Prioritized List– HERC Staff A. Upper endoscopy for GERD B. Prenatal genetic testing C. FAI surgery D. ADHD	11:00 AM
VII.	New Discussion Items – Ariel Smits A. Extracorporeal electrophoresis B. Lp-PLA2 assay	12:00 PM
VIII.	Follow Up Discussion Items – Ariel Smits 1) Intraocular steroids 2) Guideline for tonsillectomy for obstructive sleep apnea in children	12:30 PM
IX.	Public Comment	12:55 PM
X.	Adjournment – Lisa Dodson	1:00 PM

Value-based Benefits Subcommittee Recommendations Summary For Presentation to: Health Evidence Review Commission on (8/8/13)

For specific coding recommendations and guideline wording, please see the text of the 8/8/2013 VbBS minutes.

CODE MOVEMENT

- Various straightforward coding changes were made
- Procedure codes for inserting ear tubes were added to the hearing loss line for young children
- Diagnosis codes for certain conditions arising in the perinatal period were placed on the line for birth of an infant and removed from the dysfunction lines
- Fluoride varnish procedure codes were added to the preventive services lines
- Several low back pain diagnosis codes were added to an uncovered line and left on a covered line with a guideline to define when they are included on each line
- Tongue-tie was added to the feeding disorders in newborns line for the October 1, 2014 ICD-10 Prioritized List with the tongue clipping procedure. A guideline was adopted to limit this code pairing to certain issues with breast feeding.

GUIDELINE CHANGES

- The proposed High Cost Marginal Benefit Treatment guideline will not go forward
- The guideline for use of IUDs for non-contraceptive indications had one diagnosis code added
- The diagnostic guideline for non-prenatal genetic testing guideline had references updated to the most current NCCN guidelines
- The guideline note on chronic otitis media was amended to allow more liberal treatment for high risk children
- The ADHD guideline was modified to specify that parent training is first line therapy and medication is second line therapy for this condition
- The preventive dental care guideline was modified to allow fluoride varnish to be applied at well child visits with continued limits on total number of treatments allowed per year
- A new diagnostic guideline was adopted that does not allow MRI for routine surveillance in multiple sclerosis
- The guideline for treatment of cancer near the end of life was extensively revised
- The diagnostic guideline for MRI use was added back to the Prioritized List for cervical and thoracic spine imaging
- The diagnostic guideline for advanced imaging in low back pain was modified slightly to give a definition for radiculopathy
- The health behavior assessment/intervention guideline was removed
- The cystocele surgery guideline was amended to include other types of pelvic surgery other than hysterectomy and to require a trial of alternative therapy prior to surgery

- The smoking and cervical fusion guideline was amended to remove specific requirements for confirming abstinence from smoking. The guideline will continue to restrict cervical surgeries to non-smokers.
- The guideline defining neurological impairment was modified to clarify its intended meaning

ITEMS DISCUSSED THAT REQUIRE FURTHER RESEARCH

- Addition of procedure codes for installing steroid inserts into the eye to treat uveitis and central retinal vein occlusion was considered for two lines with a guideline; however, further review was requested from the P&T committee on this topic.
- A draft guideline for adenotonsillectomy for children for OSA was discussed but not adopted. Further work will be done with experts and this will be addressed at a future meeting
- A new line for the October 1, 2014 ICD-10 Prioritized List for gastrointestinal conditions in the newborn was discussed; HERC staff will work with perinatologists to refine and bring back to a later meeting.

VALUE-BASED BENEFITS SUBCOMMITTEE
Meridian Park Hospital
Community Health Education Center, Room 117B&C
Tualatin, OR
August 8, 2013
8:30 AM – 12:30 PM

Members Present: Lisa Dodson, MD, Chair; Kevin Olson, MD, Vice-chair; James Tyack, DMD; David Pollack MD; Mark Gibson (via phone); Irene Crosswell RPh; Laura Ocker, Lac; Susan Williams, MD.

Members Absent:

Staff Present: Darren Coffman; Ariel Smits, MD, MPH; Paige Hatcher, MD, MPH; Jason Gingerich.

Also Attending: Denise Taray and Wally Shaffer, MD, DMAP; Jesse Little, Actuarial Services Unit, OHA; Karen Campbell, Jennifer Stoll and Camille Kerr, Allergan; BJ Cavnor, NW Patient Education Network; Bill Voegtli and Don Harng, Novartis; Jason Parks and Hannah Bachmann, ACS CAN; Kristina Hermach, BMS; Jim Gardner, PhRMA; Nate Miles, Mary Stumnph and Kevin Pedigo, Lilly; Jean Hanekotts, Gillian Meyers, Annie Leary, Kelsey Mattsen; Elizabeth D'Amelio-Bidleman, Scott Bartle, Molly McKinley and Nicole Frager, OHSU; Dennis MacNannay, Oregon Bio Assoc; Mark Duddy and David Borhan, GNE.

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

The meeting was called to order at 8:30 am and roll was called. Minutes from the May 2013 VbBS meeting were reviewed and approved without changes.

ACTION: HERC staff will post the approved minutes on the website as soon as possible.

Smits reported on current topics proposed for the next biennial review which begins in October and will be complete by June, 2014. Current topics include: 1) open wound of eardrum, 2) fibromyalgia, 3) low back pain line structure, and 4) moving certain gastrointestinal conditions from line 692 to a new, low priority line. Other suggestions for topics for the biennial review are welcome.

Coffman discussed that HERC and P&T Committee staffs have determined that the High Cost Marginal Benefit guideline which was approved in concept by the VBBS should not go forward. It is felt that P&T's process for prior authorization was a more appropriate process for dealing with these types of medications. The current P&T process is already in place, and there is no need to involve the

Prioritized List. Irene Croswell indicated that she would be available and willing to observe and contribute to P&T meetings if needed as part of this process.

MOTION: To approve not moving forward with the High Cost Marginal Benefit Treatment Guideline. CARRIES 8-0.

Pollack asked HERC staff how DSM-5 was going to be incorporated into the Prioritized List. HERC staff agreed to form an advisory panel on behavioral health to review DSM-5 and its effects on the Prioritized List and bring back any suggested changes required.

➤ **Topic: Straightforward/Consent Agenda**

Discussion: Smits reviewed the topics on the consent agenda. One item was discussed. The procedure codes for correction of dislocated shoulders was added to one line, but left on the current lines, not deleted as noted in the meeting materials. There was no other discussion.

MOTION: To approve the all suggested changes, with the one amended shoulder dislocation procedure code placement. CARRIES 8-0

Actions:

- 1) Add 51102 to line 88
- 2) Add 25310 to line 216
- 3) Add 38571 and 38572 to line 252
- 4) Advise DMAP to remove 38571 and 38572 from the Diagnostic Procedure File
- 5) Add 20610 to line 326
- 6) Add 94640 to line 424
- 7) Add 46900-46924 to line 165
- 8) Add 25652 to line 143
- 9) Add 15004, 15005, 15040, 15115, 15116, 15120, 15121, 15135, 15136, 15155-15157, 15240, 15241 to line 91
- 10) Add 15120-15121 to line 292
- 11) Add 31237 to line 312
- 12) Add 17272-17276 to line 275
- 13) Add 35476 to line 87
- 14) Add 44055 to line 48
- 15) Add 31545-31561 to line 49
- 16) Add 77301 to line 340
- 17) Add 27598 to line 271
- 18) Add 25210 and 25215 to line 384
- 19) Add 23650-23680 to line 443
- 20) Advise DMAP to place 43653 on the Ancillary List
- 21) Remove 43653 from lines 78, 111, 409
- 22) Add 20600 and 20610 to line 326

- 23) Add 29445 to line 410
- 24) Add 33910 and 33915 to line 226
- 25) Remove 33910 and 33915 from line 385
- 26) Add 37204 to line 62
- 27) Add 38564 to line 123
- 28) Add 50840 to line 186
- 29) Add 58562 to line 448
- 30) Add 33223 to line 308
- 31) Add 19328 to line 308
- 32) Add 26990 and 27603 to line 448
- 33) Add 36825, 36830, 37205, 37206, 37208, and 37607 to line 308
- 34) Add 49423 to line 308
- 35) Add 35471, 35472, 37182, and 37183 to line 308
- 36) Add 15002-15005 and 15100-15101 to line 308
- 37) Add V20.2 to line 4
- 38) Add 736.1 to line 406
- 39) Remove 736.1 from line 407 and 550
- 40) Add 626.8 to line 446
- 41) Add 626.8 to Guideline Note 88 (see Appendix A)
- 42) Add 97140 to line 493
- 43) Remove 99241-99245 and 99251-99255 from all lines on the List
- 44) Advise DMAP to place 99241-99245 and 99251-99255 on the Excluded List
- 45) Add 10160 to lines 308 and 509
- 46) Add 14301 and 14302 to line 197
- 47) Add 38100 to line 349
- 48) Add 69110, 69120, 69145, 69150 and 69155 to line 207
- 49) Add 37205 and 37206 to lines 308 and 331
- 50) Add 61885 and 61886 to line 308
- 51) Add 426.82 to line 304
- 52) Remove 426.82 from line 376
- 53) Add 31780 and 31781 to line 49
- 54) Add 20680 to line 467
- 55) Add 649.0x to line 6
- 56) Add 38700 to line 312
- 57) Add 64719 to line 216
- 58) Add 97022 to line 216
- 59) Add 626.8 to line 446
- 60) Change condition description for line 78 to NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES
- 61) Add V55.0-V55.4 to line 78 and advise DMAP to remove from the Ancillary List
- 62) Remove V55.5 and V55.6 from lines 96 and 351
- 63) Add V55.8 to line 78 and advise DMAP to remove from the Excluded List
- 64) Amend the non-prenatal genetic testing guideline as shown in Appendix A

- 65) Add 35500-35571, 35601-35671 to line 308
- 66) Add 345.9x to line 182
- 67) Various changes made to coding specifications to convert them from ICD-9 to ICD-10
- 68) Advise DMAP to place R49.0 on the Diagnostic List
- 69) Place J38.3 on Line 564 of the October, 2014 Prioritized List and keep on line 209
 - a. Add the following coding specification to lines 209 and 564
 - i. "ICD-10 J38.3 is included on line 209 for treatment of abscesses and cellulitis of the vocal cords; it is included on line 583 for treatment of spastic dysphonia,"
 - b. Delete the current coding specification on line 209
 - i. ~~Spastic dysphonia (478.79) is not included on this line, but on Line 583~~
 - c. Add the following coding specification to line 564
 - i. "R49.0 is located on the Diagnostic List for use for the work-up of hoarseness."

➤ **Topic: Changes to the Prioritized List to Comply with the Coverage Guidance on Chronic Otitis Media in Children**

Discussion: HERC staff had been charged at the May meeting with working with Dodson to refine language for guideline note 51 to bring it into agreement with the HERC coverage guidance on chronic otitis media in children. The revised wording was presented. There was no discussion.

Actions:

- 1) Guideline note 51 was amended as shown in Appendix A
- 2) Add tympanostomy CPT codes (69424, 69433, 69436) to Line 383

➤ **Topic: Changes to the Prioritized List to Comply with the Coverage Guidance on Treatment of ADHD in Children**

Discussion: Changes to the ADHD guideline were presented that are required to bring it into agreement with the HERC coverage guidance. There was no discussion.

Actions:

- 1) Guideline note 20 modified as shown in Appendix A

➤ **Topic: Implantable intraocular steroids**

Discussion: Use of intraocular steroids for various eye conditions was presented. The initial request for review had come from an ophthalmologist and concerned the use of fluocinolone acetonide intravitreal implant (Retisert). The evidence for the use of this treatment, and a P&T Committee report on its use were reviewed. As part of these reviews, the use of a similar treatment, dexamethasone intravitreal implant (Ozurdex), was reviewed.

A representative from Allergan testified that the dexamethasone intravitreal implant (Ozurdex) uses CPT code 67028 for use, as it is simply injected with a needle. This procedure is much less costly and the implant itself is much less costly than fluocinolone acetonide intravitreal implant (Retisert), which uses CPT code 67027 for billing its insertion. Allergan is requesting that 67028 be added to lines 106 and 465 to allow this less expensive option to be used. Allergan also requested that the guideline proposed for line 106 be modified to not require systemic steroid therapy before use of Ozurdex, as this treatment is less toxic and has fewer side effects than systemic therapy. The Allergan representative also pointed out that only Ozurdex has been approved by the DFA for central retinal vein occlusion, and therefore recommended that 67027 not be added to line 465.

The subcommittee had questions about whether the presented P&T drug review was specific for Retisert or whether it included Ozurdex. Specifically, the group wants information on the complications of Ozurdex and whether systemic steroid use should be a prior requirement to its use.

Actions:

- 1) HERC staff will work with P&T staff and bring this topic back in October

➤ **Topic: Conditions arising in the perinatal period**

Discussion: A document outlining clarifying changes to the Prioritized List around ICD-9 codes 760-765 was introduced. There was no discussion.

Actions:

- 1) Add 760-762, and 764 to line 2 and remove from lines 78,318,375, and 407
- 2) Remove 765.0, 765.1, and 765.2 from lines 78,318,375, and 407
- 3) Add 765.2 to line 2

➤ **Topic: Fluoride varnish**

Discussion: A document recommending the addition of fluoride varnish CPT codes to the preventive services lines was reviewed. The subcommittee

requested clarification that these codes could not be used for application of silver nitrate or other non-fluoride varnish treatments; it was clarified that they could not.

Actions:

- 1) Add D1206 to lines 3 and 4 of the current list
 - a. Add to line 3 (Preventive services with evidence of effectiveness) for the ICD-10 Prioritized List
- 2) Modify Guideline Note 17 as shown in Appendix A

➤ **Topic: Surveillance MRI in multiple sclerosis**

Discussion: A document summarizing data which does not support use of MRI for routine surveillance in MS was reviewed. There was no discussion

Actions:

- 1) A new diagnostic guideline was adopted as shown in Appendix B

➤ **Topic: Guideline for treatment of cancer near the end of life**

Discussion: Smits gave a summary of the history of cancer treatment in the Prioritized List, as well as the current guideline, which needs to be revised due to Affordable Care Act (ACA) statutory language. She reviewed the proposed new guideline wording, and reviewed the workgroup meetings that developed the guideline. Olson gave a presentation on cancer care in the Prioritized List and how care under the new guideline would align with standard care provided to commercially insured patients. Access to timely appeals was also discussed.

Testimony: Testimony from the American Cancer Society, a patient advocacy group, and PhRMA were heard. Testimony was heard that ACA prohibits using functional status as determination for access to medication. This assertion was questioned by the subcommittee, which noted that a lawyer specializing in health care law was part of the group that drafted the new guideline. Questions were raised about palliative care provision. Palliative care is intended for coverage as is currently the case. A petition signed by over 700 citizens from Change.org was presented to the subcommittee. Most of the comments in this document appeared to relate to the previous version of Guideline Note 12 (GN12) on cancer treatment near the end of life that is being recommended to be replaced. PhRMA requests deleting GN12 and having no restrictions on cancer care. One testifier requested that an outside medical ethicist to be a part of process. Pollack noted that he is a senior fellow at the OHSU enter for Medical Ethics and teaches a course on medical ethics and therefore can act in the role of a medical ethicist for this process.

Olson noted that the subcommittee had several choices:

- end all restrictions for access to cancer chemotherapy. This is not consistent with how certain treatments for other conditions are restricted on the Prioritized List.
- 2) go ahead with the guideline revisions as proposed and see how the federal government responds to this. This would result in further discussion with the federal agencies and within the state.
- 3) do a thorough drug-by-drug review of when coverage would be allowed, perhaps limiting it to only FDA approved indications. This would be costly and likely result in more restrictions than the current proposed revised guideline.

Pollack noted that the Prioritized List has had conflicts with federal rules and regulations which have been resolved in the past or allowed under waivers. Dodson noted that some of these treatments result in harms to patients. Ocker supported the new guideline as written, noting that it was humane and fair. Gibson noted that the current guideline could be modified to keep the same intent and bring it into compliance with the ACA if found to be in conflict. Olson pointed out that many medical conditions have restrictions to some treatments according to the List.

MOTION: To approve the proposed new guideline as presented. CARRIES 8-0.

Actions:

- 1) Guideline Note 12 was amended as shown in Appendix A

➤ **Topic: Advanced imaging for back pain guideline note correction**

Discussion: A document outlining the need to re-instate the diagnostic guideline for MRI of the back for cervical and thoracic spine areas as well as make minor changes to the guideline for advanced imaging of the spine was reviewed. Williams requested that the diagnostic guideline be changed slightly to agree with the advanced imaging guideline in terms of defining abnormal reflexes.

Actions:

- 1) The diagnostic guideline for MRI of the back was re-instated as shown in Appendix B
- 2) The diagnostic guideline for advanced back imaging was modified as shown in Appendix A

➤ **Topic: Health and behavior assessment/intervention code guideline**

Discussion: DMAP and AMH have requested that the health and behavior assessment and intervention code guideline be deleted to allow better integration of physical and mental health services in CCOs. There was no discussion.

Actions:

- 1) Delete Guideline Note 1, HEALTH AND BEHAVIOR ASSESSMENT/INTERVENTION

➤ **Topic: Cystocele repair**

Discussion: Suggested changes to the cystocele repair guideline to widen it to include other pelvic floor repairs and add pre-requirements was introduced. There was some discussion about putting the pregnancy test requirement only in the hysterectomy section; however, the group felt that this was a reasonable test to get prior to other pelvic surgeries, as these surgeries are generally elective and a pregnancy may change surgical plans.

Actions:

- 1) Guideline note 50 was amended as shown in Appendix A

➤ **Topic: Cervical fusion and smoking**

Discussion: A document outlining issues with the guideline restricting back fusion surgery to non-smokers was introduced. The guideline will continue to restrict cervical surgeries to non-smokers. There was discussion about how long a patient should be abstinent from cigarettes—6 months, 12 months, etc. There were no studies done on length of time of abstinence. The subcommittee agreed with staff to continue to use 6 months, which is consistent with the bariatric surgery guideline. There was discussion about whether just smoking should be restricted, or all nicotine containing products. The subcommittee agreed that the evidence was just for smoking. There was also discussion about how to implement ensuring abstinence from smoking. The subcommittee felt that this implementation step should be left up to the plans/DMAP.

Actions:

- 1) The smoking and vertebral fusion guideline was amended as shown in Appendix A

➤ **Topic: Guideline for adenotonsillectomy for children with OSA**

Discussion: Recommended amendments for the guideline on adenotonsillectomy for obstructive sleep apnea (OSA) in children were reviewed

based on a workgroup meeting. Smits informed the subcommittee that this was informational only, and that the workgroup had another meeting scheduled. There were no comments or concerns raised by members on the work done to date.

Actions:

- 1) HERC staff will continue to work with ENT providers, health plan medical directors, and primary care providers to draft a guideline for adenotonsillectomy for children with OSA

➤ **Topic: Disorders of spine with neurologic impairment**

Discussion: A document was reviewed with suggested changes to Guideline Note 37 to clarify its intent. Additionally, certain ICD-9 codes were suggested to be added to line 562 and kept on line 400 to indicate the intent of the HERC that these conditions are only on the upper line/covered when the criteria in GN 37 are met.

Actions:

- 1) Add ICD-9 336.0, 349.2, 722.70-722.73, 723.4, 724.4 and 742.59 to line 562
- 2) Modify GN 37 as shown in Appendix A

➤ **Topic: Perinatal gastrointestinal conditions**

Discussion: A document outlining a new perinatal gastrointestinal conditions line for the October 1, 2014 Prioritized List was introduced. The subcommittee objected to possibly serious diagnoses such as peptic ulcer of the newborn and newborn reflux on a line with a very low priority. These conditions are present for non-newborns on other lines on the List. HERC staff was directed to work with perinatologists to determine if these diagnoses are not serious and can be on the new line, or if they should be included on lines with similar diagnoses for older patients. The subcommittee felt that the GERD diagnosis should possibly be on the feeding disorders line for newborns not gaining weight due to the condition.

Actions:

- 1) HERC staff will work with perinatologists and bring this topic back to a future meeting.

Topic: Frenectomy for tongue-tie

Discussion: A document was introduced with recommendations to add coverage for frenectomy for newborns with breast feeding issues. There was minimal discussion.

Actions:

- 1) Add CPT 41010 to October 1, 2014 ICD10 Prioritized List Line 19, FEEDING PROBLEMS IN NEWBORNS
- 2) Add ICD-10 Q38.1 (Ankyloglossia) to line 19 and keep on line 610 of the ICD-10 Prioritized List
- 3) Adopt a new guideline as shown in Appendix B

➤ **Public Comment**

No additional public comment was received

➤ **Issues for next meeting**

- Follow up on implantable intraocular steroids
- Follow up on perinatal gastrointestinal conditions
- Guideline for adenotonsillectomy for children with obstructive sleep apnea
- Prioritization of fibromyalgia
- Open wound of eardrum prioritization
- Low back pain line structure
- Various straightforward coding changes

➤ **Next meeting:**

Scheduled for October 10, 2013 at the Meridian Park Hospital Community Health Education Center, Rooms 117B&C with times to be determined.

Appendix A

Modified Guidelines Effective October 1, 2013

DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE

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

- A) Related to genetic testing for patients with breast/ovarian and colon/endometrial cancer 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 and endometrial cancer) services (CPT 81292-81300, 81317-81319) and familial adenomatous polyposis (FAP) services (CPT 81201-81203) should be provided as defined by the NCCN Clinical Practice Guidelines in Oncology. Colorectal Cancer Screening. V.1.2013 2.2012 (4/27/12 5/13/13). www.nccn.org
 - b) BRCA1/BRCA2 testing services (CPT 81211-81217) for women without a personal history of breast and/or ovarian cancer should be provided to high risk women as defined in [GuideLineRef,,3] or as otherwise defined by the US Preventive Services Task Force.
 - c) BRCA1/BRCA2 testing services (CPT 81211-81217) for women with a personal history of breast and/or ovarian cancer 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. V.1.2011 (4/7/11). www.nccn.org
 - d) PTEN (Cowden syndrome) services (CPT 81321-81323) should be provided as defined by the NCCN Clinical Practice Guidelines in Oncology. Colorectal Screening. V.1.2013 2.2012 (4/27/12 5/13/13). www.nccn.org.
 - 2) Genetic counseling should precede genetic testing for hereditary cancer. Very rarely, it may be appropriate for a genetic test to be performed prior to genetic counseling for a patient with cancer. If this is done, genetic counseling should be provided as soon as practical.
 - a) Pre and post-test genetic counseling by the following providers should be covered.
 - i) Medical Geneticist (M.D.) - Board Certified or Active Candidate Status from the American Board of Medical Genetics
 - ii) Clinical Geneticist (Ph.D.) - Board Certified or Active Candidate Status from the American Board of Medical Genetics.
 - iii) Genetic Counselor - Board Certified or Active Candidate Status from the American Board of Genetic Counseling, or Board Certified by the American Board of Medical Genetics.
 - iv) Advance Practice Nurse in Genetics - Credential from the Genetic Nursing Credentialing Commission.
 - 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

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- 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.
- B) 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. In 2012, this test may also be billed using one of CPT 88384-88386, or stacking CPTs 83890-83915.
 - 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. In 2012, this test may also be billed using one of CPT 88384-88386, or stacking CPTs 83890-83915.
 - 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.
- C) 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)

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- 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 81291, MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
- e) CPT 81330, SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)
- f) CPT 81350, UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, irinotecan metabolism), gene analysis, common variants (eg, *28, *36, *37)
- g) CPT 81355, VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variants (eg, -1639/3673)
- 2) The following tests are covered only if they meet the criteria for the Non-Prenatal Genetic Testing Algorithm AND the specified situations:
 - a) CPT 81205, BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, Maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X): Cover only when the newborn screening test is abnormal and serum amino acids are normal
 - b) Diagnostic testing for cystic fibrosis (CF)
 - i) CFTR, cystic fibrosis transmembrane conductance regulator tests. CPT 81220, 81223, 81222: For infants with a positive newborn screen for cystic fibrosis or who are symptomatic for cystic fibrosis, or for clients that have previously been diagnosed with cystic fibrosis but have not had genetic testing, CFTR gene analysis of a panel containing at least the mutations recommended by the American College of Medical Genetics* (CPT 81220) is covered. If two mutations are not identified, CFTR full gene sequencing (CPT 81223) is covered. If two mutations are still not identified, duplication/deletion testing (CPT 81222) is covered. These tests may be ordered as reflex testing on the same specimen.
 - c) Carrier testing for cystic fibrosis
 - i) CFTR gene analysis of a panel containing at least the mutations recommended by the American College of Medical Genetics* (CPT 81220) is covered.
 - d) 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 thromboembolism; for asymptomatic family members of patients with

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venous thromboembolism and a Factor V Leiden or Prothrombin 20210G>A mutation; or for determining the etiology of recurrent fetal loss or placental abruption.

- e) 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 thromboembolism; 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 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.
 - g) CPT 81332 SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z): The alpha-1-antitrypsin protein level should be the first line test of a suspected diagnosis of AAT deficiency in symptomatic individuals with unexplained liver disease or obstructive lung disease that is not asthma or in a middle age individual with unexplained dyspnea. Generic testing or the alpha-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.
- 3) Do not cover a more expensive genetic test (generally one with a wider scope or more detailed testing) if a cheaper (smaller scope) test is available and has, in this clinical context, a substantially similar sensitivity. For example, do not cover CFTR gene sequencing as the first test in a person of Northern European Caucasian ancestry because the gene panels are less expensive and provide substantially similar sensitivity in that context.

DIAGNOSTIC GUIDELINE D4, ADVANCED IMAGING FOR LOW BACK PAIN

In patients with non-specific low back pain and no “red flag” conditions [see Table 1], imaging is not a covered service; otherwise, workup is covered as shown in the table.

Electromyography (CPT 96002-4) is not covered for non-specific low back pain.

Table 1. Low Back Pain - Potentially Serious Conditions (“Red Flags”) and Recommendations for Initial Diagnostic Work-up

Possible cause	Key features on history or physical examination	Imaging*	Additional studies*
Cancer	History of cancer with new onset of LBP	MRI	ESR
	Unexplained weight loss Failure to improve after 1 month	Lumbosacral plain radiography	

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	Age >50 years Symptoms such as painless neurologic deficit, night pain or pain increased in supine position		
	Multiple risk factors for cancer present	Plain radiography or MRI	
Spinal column infection	Fever Intravenous drug use Recent infection	MRI	ESR and/or CRP
Cauda equina syndrome	Urinary retention Motor deficits at multiple levels Fecal incontinence Saddle anesthesia	MRI	None
Vertebral compression fracture	History of osteoporosis Use of corticosteroids Older age	Lumbosacral plain radiography	None
Ankylosing spondylitis	Morning stiffness Improvement with exercise Alternating buttock pain Awakening due to back pain during the second part of the night Younger age	Anterior-posterior pelvis plain radiography	ESR and/or CRP, HLA-B27
Nerve compression/disorders (e.g. herniated disc with radiculopathy)	Back pain with leg pain in an L4, L5, or S1 nerve root distribution present < 1 month Positive straight-leg-raise test or crossed straight-leg-raise test	None	None
	Radiculopathic symptoms** present >1 month Severe/progressive neurologic deficits (such as foot drop), progressive motor weakness	MRI***	Consider EMG/NCV
Spinal stenosis	Radiating leg pain Older age Pain usually relieved with sitting (Pseudoclaudication a weak predictor)	None	None
	Spinal stenosis symptoms present >1 month	MRI**	Consider EMG/NCV

* Level of evidence for diagnostic evaluation is variable

** Radiculopathic symptoms are defined for the purposes of this guideline as in Guideline Note 37 with any 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

*** Only if patient is a potential candidate for surgery or epidural steroid injection

Red Flag: Red flags are findings from the history and physical examination that may be associated with a higher risk of serious disorders. CRP = C-reactive protein; EMG = electromyography; ESR = erythrocyte sedimentation rate; MRI = magnetic resonance imaging; NCV = nerve conduction velocity.

Extracted and modified from Chou R, Qaseem A, Snow V, et al: Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007; 147:478-491.

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GUIDELINE NOTE 12, TREATMENT OF CANCER WITH LITTLE OR NO BENEFIT PROVIDED NEAR THE END OF LIFE

Lines 102,103,123-125,144,159,165,166,170,181,197,198,207,208,218,220,221,228,229,231,243,249,252,275-278,280,287,292,310-312,320,339-341,356,459,586,622

~~This guideline only applies to patients with advanced cancer who have less than 24 months median survival with treatment.~~

~~All patients receiving end of life care, either with the intent to prolong survival or with the intent to palliate symptoms, should have/be engaged with palliative care providers (for example, have a palliative care consult or be enrolled in a palliative care program). 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 health, 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 with any of the following: who have progressive metastatic cancer with~~

- ~~1. Median survival of less than 6 months with or without treatment, as supported by the 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~~

- ~~• a continued decline in spite of best available published evidence~~
- ~~• Median survival with treatment of 6-12 months when the treatment is expected to improve median survival by less than 50%, as supported by the best available published evidence~~
- ~~• Median survival with treatment of more than 12 months when the treatment is expected to improve median survival by less than 30%, as supported by the best available published evidence~~
- ~~• Poor prognosis with treatment, due to limited physical reserve or the ability to withstand treatment regimen, as indicated by low therapy with a non reversible Karnofsky Performance Status or Palliative Performance score of <50% with ECOG performance status.~~

- ~~2. Unpublished evidence may be taken into consideration in the case of rare cancers of 3 or higher which are universally fatal within six months without treatment, not due to a pre-existing disability.~~

~~The Health Evidence Review Commission is reluctant to place a strict \$/QALY (quality adjusted life year) or \$/LYS (life year saved) requirement on end of life treatments, as~~

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~~such measurements are only approximations and cannot take into account all of the merits of an individual case. However, cost must be taken into consideration when considering treatment options near the end of life. For example, in no instance can it be justified to spend \$100,000 in public resources to increase an individual's expected survival by three months when hundreds of thousands of Oregonians are without any form of health insurance.~~

~~Treatment with the goal to palliate is addressed~~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.

GUIDELINE NOTE 17, PREVENTIVE DENTAL CARE

Lines 3,4,58

~~Dental cleaning and fluoride treatments are~~ is limited to once per 12 months for adults and twice per 12 months for children up to age 19 (D1110, D1120, D1203, D1204, D1206). More frequent dental cleanings and/or fluoride treatments may be required for certain higher risk populations. Additionally, assessment (D0191) may be performed once per 12 months for adults and twice per 12 months for children up to age 19.

Fluoride varnish (D1206) is included on lines 3 and 4 for use with children 18 and younger during well child preventive care visits. Fluoride treatments (D1206 and D1208) are included on line 58 PREVENTIVE DENTAL SERVICES for use with adults and children during dental visits. The total number of fluoride applications provided in all settings is not to exceed four per twelve months for a child at high risk for dental caries and two per twelve months for a child not at high risk. The number of fluoride treatments is limited to once per 12 months for average risk adults and up to four times per 12 months for high risk adults.

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

Line 133

When using 314.9, Unspecified Hyperkinetic Syndrome, in children age 5 and under, it is appropriate only when the following apply:

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

~~For children age 3 and under, it is especially important that psychosocial interventions, including parent skills training and/or parent-child therapy, and environmental modifications, be tried prior to medication. For children over the age of 3, psychosocial interventions are important, whether the child is on medications or not.~~

First line therapy is "parent-behavior training" (i.e. Triple P (Positive Parenting of Preschoolers) Program, Incredible Years Parenting Program, Parent-Child Interaction Therapy and New Forest Parenting Program). The term "parent" refers to the child's primary care givers, regardless of biologic or adoptive relationship.

Second line therapy is pharmacotherapy.

Use of 314.9 for children age five and younger is limited to pairings with the following procedure codes with first and second line therapy as denoted above:

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

GUIDELINE NOTE 37, DISORDERS OF SPINE WITH NEUROLOGIC IMPAIRMENT

Line 40, 562

Diagnoses are included For the purpose of treatment coverage on Line 400 when neurologic impairment or radiculopathy is present, as , neurologic impairment or radiculopathy is defined as:

- A) Markedly abnormal reflexes
- B) Segmental muscle weakness
- C) Segmental sensory loss

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- D) EMG or NCV evidence of nerve root impingement
- E) Cauda equina syndrome,
- F) Neurogenic bowel or bladder
- G) Long tract abnormalities

Otherwise, disorders of spine not meeting these criteria (e.g. pain alone) fall on Line 562

GUIDELINE NOTE 50, UTERINE PELVIC ORGAN PROLAPSE SURGERY

Line 492

Hysterectomy, cystocele repair, and/or other surgery for pelvic organ prolapse may be indicated when all of the following are documented (A-E):

- A) Patient history of symptoms of pelvic prolapse such as:
 - 1) Complaints of the pelvic organs prolapsing at least to the introitus, AND
 - 2) Low back discomfort or pelvic pressure or
 - 3) Difficulty in defecating or
 - 4) Difficulty in voiding
- B) For hysterectomy:
 - 1) Nonmalignant cervical cytology, if cervix is present
 - G) 2) Assessment for absence of endometrial malignancy in the presence of abnormal bleeding
- DC) Physical examination is consistent with patient's symptoms of pelvic support defects indicating either symptomatic prolapse of the cervix, enterocele, cystocele, rectocele or prolapse of the vaginal vault
- ED) Negative preoperative pregnancy test unless patient is postmenopausal or has been previously sterilized
- E) Patient required to have 3 months of alternative therapy (e.g., pessaries or physical therapy, including bladder training, pelvic floor exercises and/or biofeedback, as available). If limited coverage of physical therapy is available, patients should be taught pelvic floor exercises by their treating provider, physical therapist or trained staff, and have documented consistent practice of these techniques over the 3 month period.

GUIDELINE NOTE 51, CHRONIC OTITIS MEDIA WITH EFFUSION

Line 383, 502

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

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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 383. Otherwise hearing loss associated with chronic otitis media with effusion (without those specific higher risk conditions) is only included on Line 502.

For coverage to be considered on either Line 383 or 502, 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.

GUIDELINE NOTE 88, USE OF PROGESTERONE CONTAINING IUDS FOR NON-CONTRACEPTIVE INDICATIONS

Lines 197,446,495

Intrauterine device (IUD) insertion and removal (CPT 58300 and 58301) are included on these lines for use only with progesterone containing IUDs. These CPT codes are covered only for 1) menorrhagia (ICD-9 626.2, 626.8); 2) for uterine protection in women taking estrogen replacement therapy after premature ovarian failure (ICD-9 256.3) or menopause (ICD-9 627); and 3) for uterine protection in women taking selective estrogen receptor modulators (SERMs).

GUIDELINE NOTE 100, SMOKING AND SPINAL FUSION

Lines 84,158,208,271,400,434,507,549,607

Non-emergent spinal arthrodesis (CPT 22532-22634) is limited to patients who are non-smoking for 6 months prior to the planned procedure, ~~as shown by three negative urine cotinine tests. Testing will, at a minimum, be conducted within one month of the surgery to confirm abstinence from smoking.~~ including testing on the day of surgery. Patients should be given access to appropriate smoking cessation therapy.

Appendix B

New Guidelines

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DIAGNOSTIC GUIDELINE DX, MRI IN MULTIPLE SCLEROSIS

MRI is a diagnostic test for multiple sclerosis and should not be used for routine monitoring of disease.

DIAGNOSTIC GUIDELINE DX, MRI OF THE SPINE (CERVICAL AND THORACIC)

MRI of the cervical and thoracic spine is covered in the following situations:

1. Recent onset of major or progressive neurologic deficit (objective evidence of markedly abnormal reflexes, dermatomal muscle weakness, dermatomal sensory loss, EMG or NCV evidence of nerve root impingement), suspected cauda equina syndrome (loss of bowel or bladder control or saddle anesthesia), or neurogenic claudication in patients who are potential candidates for surgery;
2. Clinical or radiological suspicion of neoplasm; or,
3. Clinical or radiological suspicion of infection.

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GUIDELINE NOTE XX, FRENOTOMY FOR TONGUE-TIE IN NEWBORNS

Lines 19, 604

ICD-10-CM Q38.1 (Ankyloglossia) is included on line 19 for pairing with CPT 41010 (Frenotomy) only when the ankyloglossia interferes with breastfeeding. Otherwise, ICD-10-CM Q38.1 and CPT 41010 are included on Line 604.

Section 3.0

Consent Agenda-

Straightforward Items

Straightforward Issues—October, 2013

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
50398	Change of nephrostomy or pyelostomy tube	186 URETERAL STRICTURE OR OBSTRUCTION; HYDRONEPHROSIS; HYDROURETER	DMAP is requesting that 50398 pair with 591 Hydronephrosis. 50398 is on lines 245 and 308. Most other nephrostomy codes are on line 186	Add 50398 to line 186
44186	Laparoscopy, surgical; jejunostomy (eg, for decompression or feeding)	62 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE 229 CANCER OF STOMACH	DMAP is requesting that 44186 pair with 151.0 Malignant neoplasm of stomach and with 537.0 Acquired hypertrophic pyloric stenosis. 44186 is currently on lines 48,78,111,339	Add 44186 to lines 62 and 229
43653	Laparoscopy, surgical; gastrostomy, without construction of gastric tube (eg, Stamm procedure) (separate procedure)	229 CANCER OF STOMACH	DMAP is requesting that 43653 pair with 151.9 Malignant neoplasm of stomach. 43653 is currently on lines 78,111,409.	Add 43653 to line 229
37204	Transcatheter occlusion or embolization (eg, for tumor destruction, to achieve hemostasis, to occlude a vascular malformation), percutaneous, any method, non-central nervous system, non-head or neck	459 CANCER OF GALLBLADDER AND OTHER BILIARY	DMAP is requesting that 37204 pair with 155.1 Malignant neoplasm of liver and intrahepatic bile ducts. 37204 is currently on lines 50,77,85,98, 141, 247,270,340	Add 37204 to line 459
77301	Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications	341 CANCER OF PANCREAS	DMAP is requesting that 77301 pair with 157.9 Malignant neoplasm of pancreas. 77301 is currently on >25 lines. Other radiation codes are on line 341.	Add 77301 to line 341

Straightforward Issues—October, 2013

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
77470	Special treatment procedure (eg, total body irradiation, hemibody radiation, per oral or endocavitary irradiation)	181 ACUTE NON-LYMPHOCYTIC LEUKEMIAS 276 CANCER OF ENDOCRINE SYSTEM, EXCLUDING THYROID; CARCINOID SYNDROME 356 CANCER OF PROSTATE GLAND	DMAP is requesting that 77470 pair with 164.0 Malignant neoplasm of thymus, 185 Malignant neoplasm of with prostate, 194.5 malignant neoplasm of Carotid body, and 205.00 Acute myeloid leukemia. 77470 is on >30 lines. Lines 181, 276 and 356 have other radiation treatment codes.	Add 77470 to lines 181, 276 and 356
52214	Cystourethroscopy, with fulguration (including cryosurgery or laser surgery) of trigone, bladder neck, prostatic fossa, urethra, or periurethral glands	287 CANCER OF BLADDER AND URETER	DMAP is requesting that 52214 be paired with 188.8 Malignant neoplasm of Other specified sites of bladder. 52214 is on lines 96, 351	Add 52214 to line 287
99324-99337 99339-99350	Domiciliary or rest home visit Individual physician supervision of a patient (patient not present) in home, domiciliary or rest home (eg, assisted living facility)		Rest home visit CPT codes are on approximately 550 lines on the prioritized List. However, they are not on mental health lines. DMAP is requesting that they be added to MHCD lines for use by mental health providers doing home visits for medication management.	Add 99324-99337 and 99339-99350 to MHCD lines
49904	Omental flap, extra-abdominal (eg, for reconstruction of sternal and chest wall defects)	216 DEEP OPEN WOUND, WITH OR WITHOUT TENDON OR NERVE INVOLVEMENT	DMAP is requesting that 49904 pair with 875.0 Open wound of chest wall w/o mention of complication. 49904 is on line 111.	Add 49904 to line 216

Straightforward Issues—October, 2013

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
61215	Insertion of subcutaneous reservoir, pump or continuous infusion system for connection to ventricular catheter	320 CANCER OF BRAIN AND NERVOUS SYSTEM	DMAP is requesting that 61215 pair with 198.4 Secondary Malignant neoplasm of other parts of nervous system. 61215 is on lines 22, 75, 78, 84, 318, 375, 401, 407. Similar subcutaneous reservoir codes are on line 320.	Add 61215 to line 320
54440	Plastic operation of penis for injury	216 DEEP OPEN WOUND, WITH OR WITHOUT TENDON OR NERVE INVOLVEMENT	DMAP is requesting that 54440 be paired with 878.0 Open wound of genital organs (external), including traumatic amputation- Penis w/o mention of complication. 54440 is on line 458 HYPOSPADIAS AND EPISPADIAS	Add 54440 to line 216
14000-14001 14021 14060-14061	Adjacent tissue transfer or rearrangement, trunk Adjacent tissue transfer or rearrangement, scalp, arms and/or legs; defect 10.1 sq cm to 30.0 sq cm Adjacent tissue transfer or rearrangement, eyelids, nose, ears and/or lips	64 BURN FULL THICKNESS GREATER THAN 10% OF BODY SURFACE	DMAP is requesting that 14060 be paired with 906.5 Late effect burn of eye, face, head, neck. On review, line 64 is missing several skin graft CPT codes.	Add 14000, 14001, 14021, 14060, 14061 to line 64
44015	Tube or needle catheter jejunostomy for enteral alimentation, intraoperative, any method	88 INJURY TO INTERNAL ORGANS	DMAP is requesting that 44015 pair with 863.21 Duodenum injury without mention of open wound into cavity. 44015 is currently on line 111.	Add 44015 to line 88

Straightforward Issues—October, 2013

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
42960-42962	Control oropharyngeal hemorrhage	308 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT	DMAP is requesting that 42960 and 42962 be paired with 998.11 Hemorrhage complicating a procedure. 42960 and 42962 are currently on line 84 DEEP ABSCESES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS; INTESTINAL PERFORATION. Similar code 42961 should also be included on line 308.	Add 42960-42962 to line 308
22010 22015	Incision and drainage, open, of deep abscess (subfascial), posterior spine; cervical, thoracic, or cervicothoracic lumbar, sacral, or lumbosacral	308 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT	DMAP is requesting that 22010 pair with 998.59 Other postoperative infection. 22010 is currently on lines 84,190,214.	Add 22010 and 22015 to line 308
61582	Craniofacial approach to anterior cranial fossa; extradural, including unilateral or bifrontal craniotomy, elevation of frontal lobe(s), osteotomy of base of anterior cranial fossa	84 DEEP ABSCESES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS; INTESTINAL PERFORATION	DMAP is requesting that 61582 be paired with 324.0 Intracranial abscess. 61582 is on lines 137,201,320.	Add 61582 to line 84
67039 67040	Vitrectomy, mechanical, pars plana approach; with focal endolaser photocoagulation with endolaser panretinal photocoagulation	473 DEGENERATION OF MACULA AND POSTERIOR POLE	DMAP is requesting that 67039 pair with 362.54 Macular cyst, hole, or pseudohole of retina. 67039 is on lines 106, 299, 308, 413. Other vitrectomy codes are on this line	Add 67039 and 67040 to line 473

Straightforward Guideline/Coding Specification Changes

1) Line 583 coding specification

- a. In August, 2013, the follow coding specification was added to line 583 SPASTIC DYSPHONIA. However, R49.0 is not on that line; it is on the Diagnostic List. HERC staff requests that this coding specification be removed as it is confusing.
- b. "R49.0 is located on the Diagnostic List for use for the work-up of hoarseness."
- c. Recommendation: Delete the coding specification regarding R49.0 from line 583

2) Line 33 coding specification

- a. Sleeve gastrectomy CPT code (43775) was added to this coding specification, but the name of the procedure was not also added.
- b. Recommendation: Change the coding specification as below:

CPT codes 43644-43645 and 43846-43848 (Roux-En-Y gastric bypass) and 43770-43775 (laparoscopic adjustable gastric banding [and sleeve gastrectomy](#)) are only included on this line as treatment according to the requirements in GuidelineNote 8 when paired with:

- 1) a primary diagnosis of 250.x0 or 250.x2 (Type II Diabetes with or without complication);
- 2) a secondary diagnosis of 278.00 (Obesity, Unspecified) or 278.01 (Morbid Obesity); AND,
- 3) a tertiary diagnosis code of V85.35-V85.45 (BMI $\geq$ 35).

3) Guideline note 66

- a. This guideline references an ASCCP guideline which is out of date. This guideline was significantly revised in 2013.
- b. Recommendation: Change the guideline as below:

GUIDELINE NOTE 66, CERVICAL DYSPLASIA

Line 31

Work up and treatment of cervical dysplasia should follow the American Society for Cervical Colposcopy and Pathology guidelines as published in the ~~American Journal of Obstetrics & Gynecology, October 2007~~ [Journal of Lower Genital Tract Disease, April 2013](#).

4) Coding specification for lines 295 OTHER PSYCHOTIC DISORDERS and 334 AUTISM SPECTRUM DISORDERS

- a. ICD-9 code 299.8 (Other specified pervasive developmental disorders) has several subdiagnoses. Two are psychotic disorders and should appear on line 295. One is Asperger's syndrome, and should appear on line 334
- b. Recommendation: Adopt the following coding specification for lines 295 and 334: "ICD-9 299.8x is included on line 295 for treatment of "atypical childhood psychosis" and "borderline psychosis of childhood." It is included on line 334 for treatment of Asperger's syndrome.

5) Diagnostic Guideline D4 Advanced Imaging for Low Back Pain

- a. This guideline uses the phrase "radiculopathic symptoms" twice when what is actually meant is "radiculopathic signs."
- b. Recommendation: change the two instances of "radiculopathic symptoms" to "radiculopathic signs."

Section 4.0

New Codes

2014 CPT Code Summary Document

CPT code	Code description	Similar Codes	Proposed List/Line(s)	Comments
10030	Image-guided fluid collection drainage by catheter (eg, abscess, hematoma, seroma, lymphocele, cyst), soft tissue (eg, extremity, abdominal wall, neck), percutaneous	10060-10061 Incision and drainage of abscess (eg, carbuncle, suppurative hidradenitis, cutaneous or subcutaneous abscess, cyst, furuncle, or paronychia)	84 DEEP ABSCESES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS; INTESTINAL PERFORATION 214 SUPERFICIAL ABSCESES AND CELLULITIS 250 PERIPHERAL VASCULAR DISEASE, LIMB THREATENING INFECTIONS, AND VASCULAR COMPLICATIONS 308 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 427 LYMPHADENITIS	Only lines likely to have more complicated drainage included from the lines containing 10060-10061
19081	Biopsy, breast, with placement of breast localization device(s) (eg, clip, metallic pellet), when performed, and imaging of the biopsy specimen, when performed, percutaneous; first lesion, including stereotactic guidance		Diagnostic	See Issues
19082	Biopsy, breast, with placement of breast localization device(s) (eg, clip, metallic pellet), when performed, and imaging of the biopsy specimen, when performed, percutaneous; each additional lesion, including stereotactic guidance (List separately in addition to code for primary procedure)		Diagnostic	See Issues
19083	Biopsy, breast, with placement of breast localization device(s) (eg, clip, metallic pellet), when performed, and imaging of the biopsy specimen, when performed, percutaneous; first lesion, including ultrasound guidance		Diagnostic	See Issues

2014 CPT Code Summary Document

CPT code	Code description	Similar Codes	Proposed List/Line(s)	Comments
19084	Biopsy, breast, with placement of breast localization device(s) (eg, clip, metallic pellet), when performed, and imaging of the biopsy specimen, when performed, percutaneous; each additional lesion, including ultrasound guidance (List separately in addition to code for primary procedure)		Diagnostic	See Issues
19085	Biopsy, breast, with placement of breast localization device(s) (eg, clip, metallic pellet), when performed, and imaging of the biopsy specimen, when performed, percutaneous; first lesion, including magnetic resonance guidance		Diagnostic	See Issues
19086	Biopsy, breast, with placement of breast localization device(s) (eg, clip, metallic pellet), when performed, and imaging of the biopsy specimen, when performed, percutaneous; each additional lesion, including magnetic resonance guidance (List separately in addition to code for primary procedure)		Diagnostic	See Issues
19281	Placement of breast localization device(s) (eg, clip, metallic pellet, wire/needle, radioactive seeds), percutaneous; first lesion, including mammographic guidance		Diagnostic	See Issues--Imaged Assisted Breast Biopsy
19282	Placement of breast localization device(s) (eg, clip, metallic pellet, wire/needle, radioactive seeds), percutaneous; each additional lesion, including mammographic guidance (List separately in addition to code for primary procedure)		Diagnostic	See Issues--Imaged Assisted Breast Biopsy

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CPT code	Code description	Similar Codes	Proposed List/Line(s)	Comments
19283	Placement of breast localization device(s) (eg, clip, metallic pellet, wire/needle, radioactive seeds), percutaneous; first lesion, including stereotactic guidance		Diagnostic	See Issues--Imaged Assisted Breast Biopsy
19284	Placement of breast localization device(s) (eg, clip, metallic pellet, wire/needle, radioactive seeds), percutaneous; each additional lesion, including stereotactic guidance (List separately in addition to code for primary procedure)		Diagnostic	See Issues--Imaged Assisted Breast Biopsy
19285	Placement of breast localization device(s) (eg, clip, metallic pellet, wire/needle, radioactive seeds), percutaneous; first lesion, including ultrasound guidance		Diagnostic	See Issues--Imaged Assisted Breast Biopsy
19286	Placement of breast localization device(s) (eg, clip, metallic pellet, wire/needle, radioactive seeds), percutaneous; each additional lesion, including ultrasound guidance (List separately in addition to code for primary procedure)		Diagnostic	See Issues--Imaged Assisted Breast Biopsy
19287	Placement of breast localization device(s) (eg clip, metallic pellet, wire/needle, radioactive seeds), percutaneous; first lesion, including magnetic resonance guidance		Diagnostic	See Issues--Imaged Assisted Breast Biopsy
19288	Placement of breast localization device(s) (eg clip, metallic pellet, wire/needle, radioactive seeds), percutaneous; each additional lesion, including magnetic resonance guidance		Diagnostic	See Issues--Imaged Assisted Breast Biopsy
23333	Removal of foreign body, shoulder; deep (subfascial or intramuscular)		464 RESIDUAL FOREIGN BODY IN SOFT TISSUE	

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CPT code	Code description	Similar Codes	Proposed List/Line(s)	Comments
23334	Removal of prosthesis, includes debridement and synovectomy when performed; humeral or glenoid component		308 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 443 DISORDERS OF SHOULDER,POTENTIALLY RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT	
23335	Removal of prosthesis, includes debridement and synovectomy when performed; humeral and glenoid components (eg, total shoulder)		308 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 443 DISORDERS OF SHOULDER,POTENTIALLY RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT	
33366	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; transapical exposure (eg, left thoracotomy)	33367-33369 Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve) is on the lines listed	76 ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION 90 MYOCARDITIS (NONVIRAL), PERICARDITIS (NONVIRAL) AND ENDOCARDITIS 116 CONGENITAL STENOSIS AND INSUFFICIENCY OF AORTIC VALVE 192 MULTIPLE VALVULAR DISEASE 195 CHRONIC ISCHEMIC HEART DISEASE 237 DISEASES AND DISORDERS OF AORTIC VALVE 308 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 354 COCCIDIOIDOMYCOSIS, HISTOPLASMOSIS, BLASTOMYCOTIC INFECTION, OPPORTUNISTIC AND OTHER MYCOSES	

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CPT code	Code description	Similar Codes	Proposed List/Line(s)	Comments
34841	Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including one visceral artery endoprosthesis (superior mesenteric, celiac or renal artery)	33320-33322 Suture repair of aorta or great vessels	88 INJURY TO INTERNAL ORGANS 270 ARTERIAL EMBOLISM/THROMBOSIS: ABDOMINAL AORTA, THORACIC AORTA 293 INJURY TO BLOOD VESSELS OF THE THORACIC CAVITY 307 DISSECTING OR RUPTURED AORTIC ANEURYSM 349 NON-DISSECTING ANEURYSM WITHOUT RUPTURE	
34842	Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including two visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])		88 INJURY TO INTERNAL ORGANS 270 ARTERIAL EMBOLISM/THROMBOSIS: ABDOMINAL AORTA, THORACIC AORTA 293 INJURY TO BLOOD VESSELS OF THE THORACIC CAVITY 307 DISSECTING OR RUPTURED AORTIC ANEURYSM 349 NON-DISSECTING ANEURYSM WITHOUT RUPTURE	
34843	Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including three visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])		88 INJURY TO INTERNAL ORGANS 270 ARTERIAL EMBOLISM/THROMBOSIS: ABDOMINAL AORTA, THORACIC AORTA 293 INJURY TO BLOOD VESSELS OF THE THORACIC CAVITY 307 DISSECTING OR RUPTURED AORTIC ANEURYSM 349 NON-DISSECTING ANEURYSM WITHOUT RUPTURE	

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CPT code	Code description	Similar Codes	Proposed List/Line(s)	Comments
34844	Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including four or more visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])		88 INJURY TO INTERNAL ORGANS 270 ARTERIAL EMBOLISM/THROMBOSIS: ABDOMINAL AORTA, THORACIC AORTA 293 INJURY TO BLOOD VESSELS OF THE THORACIC CAVITY 307 DISSECTING OR RUPTURED AORTIC ANEURYSM 349 NON-DISSECTING ANEURYSM WITHOUT RUPTURE	
34845	Endovascular repair of visceral aorta and infrarenal abdominal aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including one visceral artery endoprosthesis (superior mesenteric, celiac or renal artery)		88 INJURY TO INTERNAL ORGANS 270 ARTERIAL EMBOLISM/THROMBOSIS: ABDOMINAL AORTA, THORACIC AORTA 293 INJURY TO BLOOD VESSELS OF THE THORACIC CAVITY 307 DISSECTING OR RUPTURED AORTIC ANEURYSM 349 NON-DISSECTING ANEURYSM WITHOUT RUPTURE	

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CPT code	Code description	Similar Codes	Proposed List/Line(s)	Comments
34848	Endovascular repair of visceral aorta and infrarenal abdominal aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including four or more visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])		88 INJURY TO INTERNAL ORGANS 270 ARTERIAL EMBOLISM/THROMBOSIS: ABDOMINAL AORTA, THORACIC AORTA 293 INJURY TO BLOOD VESSELS OF THE THORACIC CAVITY 307 DISSECTING OR RUPTURED AORTIC ANEURYSM 349 NON-DISSECTING ANEURYSM WITHOUT RUPTURE	
37217	Transcatheter placement of an intravascular stent(s), intrathoracic common carotid artery or innominate artery by retrograde treatment, via open ipsilateral cervical carotid artery exposure, including angioplasty, when performed, and radiological supervision and interpretation	433.10 Occlusion and stenosis of carotid artery without mention of cerebral infarction is on line 440 Carotid endarterectomy (CPT 35301) is on lines 308, 342, 349, 350, 440.	308 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 342 STROKE 349 NON-DISSECTING ANEURYSM WITHOUT RUPTURE 350 ARTERIAL ANEURYSM OF NECK 440 TRANSIENT CEREBRAL ISCHEMIA; OCCLUSION/STENOSIS OF PRECEREBRAL ARTERIES WITHOUT OCCLUSION	
37236	Transcatheter placement of an intravascular stent(s) (except lower extremity, cervical carotid, extracranial vertebral or intrathoracic carotid, intracranial, or coronary), open or percutaneous, including radiological supervision and interpretation and including all angioplasty within the same vessel, when performed; initial artery		378 ATHEROSCLEROSIS, PERIPHERAL	

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CPT code	Code description	Similar Codes	Proposed List/Line(s)	Comments
37237	Transcatheter placement of an intravascular stent(s) (except lower extremity, cervical carotid, extracranial vertebral or intrathoracic carotid, intracranial, or coronary), open or percutaneous, including radiological supervision and interpretation and including all angioplasty within the same vessel, when performed; each additional artery (List separately in addition to code for primary procedure)		378 ATHEROSCLEROSIS, PERIPHERAL	
37238	Transcatheter placement of an intravascular stent(s), open or percutaneous, including radiological supervision and interpretation and including angioplasty within the same vessel, when performed; initial vein		378 ATHEROSCLEROSIS, PERIPHERAL	
37239	Transcatheter placement of an intravascular stent(s), open or percutaneous, including radiological supervision and interpretation and including angioplasty within the same vessel, when performed; each additional vein (List separately in addition to code for primary procedure)		378 ATHEROSCLEROSIS, PERIPHERAL	

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CPT code	Code description	Similar Codes	Proposed List/Line(s)	Comments
37241	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; venous, other than hemorrhage (eg, congenital or acquired venous malformations, venous and capillary hemangiomas, varices, varicoceles)	Hemangiomas (ICD-9 228.0x) on lines 106 (retinopathy--already has treatment codes), 137 (CNS, has other CPT codes), 656 Varices/varicoceles on lines 224, 570 Venous malformations on line 201 (CNS) 747.6x (vessel anomaly) is Excluded	570 SUBLINGUAL, SCROTAL, AND PELVIC VARICES 656 BENIGN NEOPLASMS OF SKIN AND OTHER SOFT TISSUES	Four new codes replace existing embolization codes of 37210 (uterine fibroid embolization) and the non-CNS, non-head embolization code, 37204. 37204 was on lines 50, 62, 77, 85, 98, 141, 247, 270 and 340. Most of these are congenital heart disease lines Separate CPT codes exist for CNS embolization (61624, 61626)
37242	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; arterial, other than hemorrhage or tumor (eg, congenital or acquired arterial malformations, arteriovenous malformations, arteriovenous fistulas, aneurysms, pseudoaneurysms)		570 SUBLINGUAL, SCROTAL, AND PELVIC VARICES 656 BENIGN NEOPLASMS OF SKIN AND OTHER SOFT TISSUES	
37243	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction		340 CANCER OF LIVER 428 UTERINE LEIOMYOMA	Only tumors previously paired with 37204 were uterine fibroids and liver cancer.

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CPT code	Code description	Similar Codes	Proposed List/Line(s)	Comments
37244	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for arterial or venous hemorrhage or lymphatic extravasation		62 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE 224 ESOPHAGEAL VARICES	All major GI hemorrhage codes (other than for colon) are on these lines
43191	Esophagoscopy, rigid, transoral; diagnostic, including collection of specimen(s) by brushing or washing when performed (separate procedure)		Diagnostic	
43192	Esophagoscopy, rigid, transoral; with directed submucosal injection(s), any substance	43201 Esophagoscopy, rigid or flexible; with directed submucosal injection(s), any substance	62 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE 224 ESOPHAGEAL VARICES 339 CANCER OF ESOPHAGUS 409 ESOPHAGEAL STRICTURE 411 ESOPHAGITIS; ESOPHAGEAL AND INTRAESOPHAGEAL HERNIAS 421 ACHALASIA, NON-NEONATAL	Note: previous esophagoscopy codes were both for rigid and flexible procedures. New codes break these two types of procedures into 2 separate codes
43193	Esophagoscopy, rigid, transoral; with biopsy, single or multiple		Diagnostic	
43194	Esophagoscopy, rigid, transoral; with removal of foreign body	43215 Esophagoscopy, rigid or flexible; with removal of foreign body	126 FOREIGN BODY IN PHARYNX, LARYNX, TRACHEA, BRONCHUS AND ESOPHAGUS	
43195	Esophagoscopy, rigid, transoral; with balloon dilation (less than 30 mm diameter)	43220 Esophagoscopy, rigid or flexible; with balloon dilation	339 CANCER OF ESOPHAGUS 409 ESOPHAGEAL STRICTURE 421 ACHALASIA, NON-NEONATAL 622 SECONDARY AND ILL-DEFINED MALIGNANT NEOPLASMS 667 BENIGN NEOPLASMS OF DIGESTIVE SYSTEM	

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CPT code	Code description	Similar Codes	Proposed List/Line(s)	Comments
43196	Esophagoscopy, rigid, transoral; with insertion of guide wire followed by dilation over guide wire	43226	339 CANCER OF ESOPHAGUS 409 ESOPHAGEAL STRICTURE 421 ACHALASIA, NON-NEONATAL 622 SECONDARY AND ILL-DEFINED MALIGNANT NEOPLASMS 667 BENIGN NEOPLASMS OF DIGESTIVE SYSTEM	
43197	Esophagoscopy, flexible, transnasal; diagnostic, includes collection of specimen(s) by brushing or washing when performed (separate procedure)		Diagnostic	
43198	Esophagoscopy, flexible, transnasal; with biopsy, single or multiple		Diagnostic	
43211	Esophagoscopy, flexible, transoral; with endoscopic mucosal resection		Diagnostic	Used for diagnosis and, in some cases, treatment of lesions such as colon polyps, stomach cancer, Barrett's esophagus
43212	Esophagoscopy, flexible, transoral; with placement of endoscopic stent (includes pre- and post-dilation and guide wire passage, when performed)	43219 Esophagoscopy, rigid or flexible; with insertion of plastic tube or stent	339 CANCER OF ESOPHAGUS 409 ESOPHAGEAL STRICTURE 421 ACHALASIA, NON-NEONATAL 622 SECONDARY AND ILL-DEFINED MALIGNANT NEOPLASMS 667 BENIGN NEOPLASMS OF DIGESTIVE SYSTEM	
43213	Esophagoscopy, flexible, transoral; with dilation of esophagus, by balloon or dilator, retrograde (includes fluoroscopic guidance, when performed)		339 CANCER OF ESOPHAGUS 409 ESOPHAGEAL STRICTURE 421 ACHALASIA, NON-NEONATAL 622 SECONDARY AND ILL-DEFINED MALIGNANT NEOPLASMS 667 BENIGN NEOPLASMS OF DIGESTIVE SYSTEM	

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CPT code	Code description	Similar Codes	Proposed List/Line(s)	Comments
43214	Esophagoscopy, flexible, transoral; with dilation of esophagus with balloon (30 mm diameter or larger) (includes fluoroscopic guidance, when performed)		339 CANCER OF ESOPHAGUS 409 ESOPHAGEAL STRICTURE 421 ACHALASIA, NON-NEONATAL 622 SECONDARY AND ILL-DEFINED MALIGNANT NEOPLASMS 667 BENIGN NEOPLASMS OF DIGESTIVE SYSTEM	
43229	Esophagoscopy, flexible, transoral; with ablation of tumor(s), polyp(s), or other lesion(s) (includes pre- and post-dilation and guide wire passage, when performed)	43216 Esophagoscopy, rigid or flexible; with ablation of tumor(s), polyp(s), or other lesion(s)	339 CANCER OF ESOPHAGUS 622 SECONDARY AND ILL-DEFINED MALIGNANT NEOPLASMS 667 BENIGN NEOPLASMS OF DIGESTIVE SYSTEM	
43233	Esophagogastroduodenoscopy, flexible, transoral; with dilation of esophagus with balloon (30 mm diameter or larger) (includes fluoroscopic guidance, when performed)		339 CANCER OF ESOPHAGUS 409 ESOPHAGEAL STRICTURE 421 ACHALASIA, NON-NEONATAL 622 SECONDARY AND ILL-DEFINED MALIGNANT NEOPLASMS 667 BENIGN NEOPLASMS OF DIGESTIVE SYSTEM	
43253	Esophagogastroduodenoscopy, flexible, transoral; with transendoscopic ultrasound-guided transmural injection of diagnostic or therapeutic substance(s) (eg, anesthetic, neurolytic agent) or fiducial marker(s) (includes endoscopic ultrasound examination of the esophagus, stomach, and either the duodenum or a surgically altered stomach where the jejunum is examined distal to the anastomosis)		Diagnostic	
43254	Esophagogastroduodenoscopy, flexible, transoral; with endoscopic mucosal resection		Diagnostic	

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CPT code	Code description	Similar Codes	Proposed List/Line(s)	Comments
43266	Esophagogastroduodenoscopy, flexible, transoral; with placement of endoscopic stent (includes pre- and post-dilation and guide wire passage, when performed)		339 CANCER OF ESOPHAGUS 409 ESOPHAGEAL STRICTURE 421 ACHALASIA, NON-NEONATAL 622 SECONDARY AND ILL-DEFINED MALIGNANT NEOPLASMS 667 BENIGN NEOPLASMS OF DIGESTIVE SYSTEM	
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)		339 CANCER OF ESOPHAGUS 622 SECONDARY AND ILL-DEFINED MALIGNANT NEOPLASMS 667 BENIGN NEOPLASMS OF DIGESTIVE SYSTEM	
43274	Endoscopic retrograde cholangiopancreatography (ERCP); with placement of endoscopic stent into biliary or pancreatic duct, including pre- and post-dilation and guide wire passage, when performed, including sphincterotomy, when performed, each stent	ERCP codes on lines 61,200,267,319,341,459,671 Some also on line 308 Some on line 196	61 CHOLELITHIASIS, CHOLECYSTITIS, COMMON BILIARY DUCT STONE 196 NEOPLASMS OF ISLETS OF LANGERHANS 200 ACUTE PANCREATITIS 267 CHRONIC PANCREATITIS 308 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 319 ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER 341 CANCER OF PANCREAS 459 CANCER OF GALLBLADDER AND OTHER BILIARY 671 GALLSTONES WITHOUT CHOLECYSTITIS	Note: all ERCP codes should probably be on line 196 and 308

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CPT code	Code description	Similar Codes	Proposed List/Line(s)	Comments
43275	Endoscopic retrograde cholangiopancreatography (ERCP); with removal of foreign body(s) or stent(s) from biliary/pancreatic duct(s)		61 CHOLELITHIASIS, CHOLECYSTITIS, COMMON BILIARY DUCT STONE 196 NEOPLASMS OF ISLETS OF LANGERHANS 200 ACUTE PANCREATITIS 267 CHRONIC PANCREATITIS 308 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 319 ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER 341 CANCER OF PANCREAS 459 CANCER OF GALLBLADDER AND OTHER BILIARY 671 GALLSTONES WITHOUT CHOLECYSTITIS	
43276	Endoscopic retrograde cholangiopancreatography (ERCP); with removal and exchange of stent(s), biliary or pancreatic duct, including pre- and post-dilation and guide wire passage, when performed, including sphincterotomy, when performed, each stent exchanged	43268 Endoscopic retrograde cholangiopancreatography (ERCP); with endoscopic retrograde insertion of tube or stent into bile or pancreatic duct	61 CHOLELITHIASIS, CHOLECYSTITIS, COMMON BILIARY DUCT STONE 196 NEOPLASMS OF ISLETS OF LANGERHANS 200 ACUTE PANCREATITIS 267 CHRONIC PANCREATITIS 308 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 319 ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER 341 CANCER OF PANCREAS 459 CANCER OF GALLBLADDER AND OTHER BILIARY 671 GALLSTONES WITHOUT CHOLECYSTITIS	

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CPT code	Code description	Similar Codes	Proposed List/Line(s)	Comments
43277	Endoscopic retrograde cholangiopancreatography (ERCP); with trans-endoscopic balloon dilation of biliary/pancreatic duct(s) or of ampulla (sphincteroplasty), including sphincterotomy, when performed, each duct	43271	61 CHOLELITHIASIS, CHOLECYSTITIS, COMMON BILIARY DUCT STONE 196 NEOPLASMS OF ISLETS OF LANGERHANS 200 ACUTE PANCREATITIS 267 CHRONIC PANCREATITIS 308 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 319 ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER 341 CANCER OF PANCREAS 459 CANCER OF GALLBLADDER AND OTHER BILIARY 671 GALLSTONES WITHOUT CHOLECYSTITIS	
43278	Endoscopic retrograde cholangiopancreatography (ERCP); with ablation of tumor(s), polyp(s), or other lesion(s), including pre- and post-dilation and guide wire passage, when performed		61 CHOLELITHIASIS, CHOLECYSTITIS, COMMON BILIARY DUCT STONE 196 NEOPLASMS OF ISLETS OF LANGERHANS 200 ACUTE PANCREATITIS 267 CHRONIC PANCREATITIS 319 ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER 341 CANCER OF PANCREAS 459 CANCER OF GALLBLADDER AND OTHER BILIARY 671 GALLSTONES WITHOUT CHOLECYSTITIS	

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CPT code	Code description	Similar Codes	Proposed List/Line(s)	Comments
49405	Image-guided fluid collection drainage by catheter (eg, abscess, hematoma, seroma, lymphocele, cyst); visceral (eg, kidney, liver, spleen, lung/mediastinum), percutaneous		84 DEEP ABSCESSSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS; INTESTINAL PERFORATION 308 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 427 LYMPHADENITIS	See 10030 above
49406	Image-guided fluid collection drainage by catheter (eg, abscess, hematoma, seroma, lymphocele, cyst); peritoneal or retroperitoneal, percutaneous		84 DEEP ABSCESSSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS; INTESTINAL PERFORATION 308 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 427 LYMPHADENITIS	
49407	Image-guided fluid collection drainage by catheter (eg, abscess, hematoma, seroma, lymphocele, cyst); peritoneal or retroperitoneal, transvaginal or transrectal		84 DEEP ABSCESSSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS; INTESTINAL PERFORATION 308 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 427 LYMPHADENITIS	
52356	Cystourethroscopy, with ureteroscopy and/or pyeloscopy; with lithotripsy including insertion of indwelling ureteral stent (eg, Gibbons or double-J type)	52353 Cystourethroscopy, with ureteroscopy and/or pyeloscopy; with lithotripsy (ureteral catheterization is included) is on 54, 186, 379	54 CONGENITAL HYDRONEPHROSIS 186 URETERAL STRICTURE OR OBSTRUCTION; HYDRONEPHROSIS; HYDROURETER 379 URINARY SYSTEM CALCULUS	

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CPT code	Code description	Similar Codes	Proposed List/Line(s)	Comments
64616	Chemodenervation of muscle(s); neck muscle(s), excluding muscles of the larynx, unilateral (eg, for cervical dystonia, spasmodic torticollis)	333.83 (Spasmodic torticollis) and dystonic are on line 388. 64613, 64614 (codes being replaced by 64616 and 64617) are on line 388	388 DYSTONIA (UNCONTROLLABLE); LARYNGEAL SPASM AND STENOSIS	Change coding specification on line 388 to read: "Chemodenervation with botulinum toxin injection (CPT 64612, ~~64614~~ , 64616) is included on this line only for treatment of blepharospasm (ICD-9 333.81), spasmodic torticollis (ICD-9 333.83), and other fragments of torsion dystonia (ICD-9 333.89).
64617	Chemodenervation of muscle(s); larynx, unilateral, percutaneous (eg, for spasmodic dysphonia), includes guidance by needle electromyography, when performed		Excluded	Chemodenervation of larynx for spastic dysphonia was reviewed in December, 2009 and found to not have sufficient evidence to be added as a treatment on the Prioritized List.

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CPT code	Code description	Similar Codes	Proposed List/Line(s)	Comments
64642	Chemodenervation of one extremity; 1-4 muscle(s)	64614 (Chemodenervation of extremity and/or trunk muscle) (e.g. for dystonia, cerebral palsy, multiple sclerosis) was on line 388 and 318 (replaced by this new code)	318 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS	
64643	Chemodenervation of one extremity; each additional extremity, 1-4 muscle(s) (List separately in addition to code for primary procedure)		318 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS	
64644	Chemodenervation of one extremity; 5 or more muscle(s)		318 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS	
64645	Chemodenervation of one extremity; each additional extremity, 5 or more muscle(s) (List separately in addition to code for primary procedure)		318 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS	
64646	Chemodenervation of trunk muscle(s); 1-5 muscle(s)		318 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS	
64647	Chemodenervation of trunk muscle(s); 6 or more muscle(s)		318 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS	
66183	Insertion of anterior segment aqueous drainage device, without extraocular reservoir, external approach	66180 (Aqueous shunt to extraocular reservoir) is on lines 149,258	149 GLAUCOMA, OTHER THAN PRIMARY ANGLE-CLOSURE 258 PRIMARY ANGLE-CLOSURE GLAUCOMA	

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CPT code	Code description	Similar Codes	Proposed List/Line(s)	Comments
77293	Respiratory motion management simulation (List separately in addition to code for primary procedure)	Add on for code 77301. 77301 found on suggested lines.	102,124,136,137,140,144, 162, 165, 166, 197, 207, 208, 218, 220, 221, 229, 243, 249, 275, 276, 278, 287, 292, 312, 320, 339, 340, 342, 356, 466, 549, 622, 633	Used in radiation oncology to increase tissue sparing. Must be used as an add-on code to either CPT code 77295 or 77301
80155	Caffeine		Diagnostic	
80159	Clozapine		Diagnostic	
80169	Everolimus		Diagnostic	
80171	Gabapentin		Diagnostic	
80175	Lamotrigine		Diagnostic	
80177	Levetiracetam		Diagnostic	
80180	Mycophenolate (mycophenolic acid)		Diagnostic	
80183	Oxcarbazepine		Diagnostic	
80199	Tiagabine		Diagnostic	
80203	Zonisamide		Diagnostic	
81161	DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed		Diagnostic	See Issues--Genetic Testing
81287	MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme), methylation analysis		Excluded	See Issues--Genetic Testing
81504	Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores		Excluded	See Issues--Genetic Testing
81507	Fetal aneuploidy (trisomy 21, 18, and 13) DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy		1 PREGNANCY	reviewed in prenatal genetic testing coverage guidance process.

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CPT code	Code description	Similar Codes	Proposed List/Line(s)	Comments
87661	Infectious agent detection by nucleic acid (DNA or RNA); Trichomonas vaginalis, amplified probe technique		Diagnostic	
88343	Immunohistochemistry or immunocytochemistry, each separately identifiable antibody per block, cytologic preparation, or hematologic smear; each additional separately identifiable antibody per slide (List separately in addition to code for primary procedure)		Diagnostic	
90673	Influenza virus vaccine, trivalent, derived from recombinant DNA (RIV3), hemagglutinin (HA) protein only, preservative and antibiotic free, for intramuscular use		424 INFLUENZA	
90685	Influenza virus vaccine, quadrivalent, split virus, preservative free, when administered to children 6-35 months of age, for intramuscular use		424 INFLUENZA	
90686	Influenza virus vaccine, quadrivalent, split virus, preservative free, when administered to individuals 3 years of age and older, for intramuscular use		424 INFLUENZA	
90687	Influenza virus vaccine, quadrivalent, split virus, when administered to children 6-35 months of age, for intramuscular use		424 INFLUENZA	
90688	Influenza virus vaccine, quadrivalent, split virus, when administered to individuals 3 years of age and older, for intramuscular use		424 INFLUENZA	

2014 CPT Code Summary Document

CPT code	Code description	Similar Codes	Proposed List/Line(s)	Comments
92521	Evaluation of speech fluency (eg, stuttering, cluttering)	replacing 92506 (Evaluation of speech, language, voice, communication, and/or auditory processing)	64, 75, 80, 100, 101, 185, 201, 202, 273, 289, 308, 312, 325, 342, 375, 448	
92522	Evaluation of speech sound production (eg, articulation, phonological process, apraxia, dysarthria);		64, 75, 80, 100, 101, 185, 201, 202, 273, 289, 308, 312, 325, 342, 375, 448	
92523	Evaluation of speech sound production (eg, articulation, phonological process, apraxia, dysarthria); with evaluation of language comprehension and expression (eg, receptive and expressive language)		64, 75, 80, 100, 101, 185, 201, 202, 273, 289, 308, 312, 325, 342, 375, 448	
92524	Behavioral and qualitative analysis of voice and resonance		64, 75, 80, 100, 101, 185, 201, 202, 273, 289, 308, 312, 325, 342, 375, 448	
93582	Percutaneous transcatheter closure of patent ductus arteriosus	747.0 (Patent ductus arteriosus) on lines 85, 256. 256 is a transplant line	85 PATENT DUCTUS ARTERIOSUS; AORTIC PULMONARY FISTULA	
93583	Percutaneous transcatheter septal reduction therapy (eg, alcohol septal ablation) including temporary pacemaker insertion when performed		109 CARDIOMYOPATHY, HYPERTROPHIC MUSCLE	See Issues-- Procedures
94669	Mechanical chest wall oscillation to facilitate lung function, per session		26 CYSTIC FIBROSIS 65 BRONCHIECTASIS 78 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES	See Issues-- Procedures

2014 CPT Code Summary Document

CPT code	Code description	Similar Codes	Proposed List/Line(s)	Comments
97610	Low frequency, non-contact, non-thermal ultrasound, including topical application(s), when performed, wound assessment, and instruction(s) for ongoing care, per day		Excluded List	See Issues--Procedures
99446	Interprofessional telephone/Internet assessment and management service provided by a consultative physician including a verbal and written report to the patient's treating/requesting physician or other qualified health care professional; 5-10 minutes of medical consultative discussion and review		E&M lines (inpatient and outpatient)	
99447	Interprofessional telephone/Internet assessment and management service provided by a consultative physician including a verbal and written report to the patient's treating/requesting physician or other qualified health care professional; 11-20 minutes of medical consultative discussion and review		E&M lines (inpatient and outpatient)	
99448	Interprofessional telephone/Internet assessment and management service provided by a consultative physician including a verbal and written report to the patient's treating/requesting physician or other qualified health care professional; 21-30 minutes of medical consultative discussion and review		E&M lines (inpatient and outpatient)	

2014 CPT Code Summary Document

CPT code	Code description	Similar Codes	Proposed List/Line(s)	Comments
99449	Interprofessional telephone/Internet assessment and management service provided by a consultative physician including a verbal and written report to the patient's treating/requesting physician or other qualified health care professional; 31 minutes or more of medical consultative discussion and review		E&M lines (inpatient and outpatient)	
99481	Total body systemic hypothermia in a critically ill neonate per day (List separately in addition to code for primary procedure)		E&M lines (inpatient)	
99482	Selective head hypothermia in a critically ill neonate per day (List separately in addition to code for primary procedure)		E&M lines (inpatient)	

2014 CPT Code Review Issues

Image Assisted Breast Biopsies

Image assisted breast biopsies (CPT 19081-19086), placement of breast lesion localization devices (**19281-19288**)

- 1) Definition: techniques used for the diagnosis of lesions seen on breast cancer screening (mammogram, ultrasound, breast MRI).
- 2) Literature
 - a. **Bruening 2010**, review comparing image assisted needle biopsies with open biopsies of suspicious breast lesions
 - i. Concluded that Stereotactic- and ultrasonography-guided core-needle biopsy procedures seem to be almost as accurate as open surgical biopsy, with lower complication rates.
 - b. **O'Flynn 2010**, review of breast biopsy techniques
 - i. Ultrasound is the preferred first-line mode for image guided breast biopsy. It is well accepted, quick, readily accessible, and less costly than other localization techniques without the need for ionizing radiation.
 - ii. Stereotactic breast biopsies are performed when suspicious lesions are seen on mammography but cannot be visualized with ultrasound. They are performed most commonly for microcalcifications
 - iii. MRI guided biopsies: have a role for certain difficult to visualize lesions. The cost and time taken up on the MRI machine is high, making it only a necessity in cases where the lesion is not seen on mammography or ultrasound.
 - c. **Vandromme 2011**, review of breast biopsy techniques
 - i. image-guided percutaneous biopsy methods have flourished and continue to be modified to yield higher accuracy with fewer underestimations and false-negative findings and as a result are the preferred method of obtaining a diagnosis for suspicious breast lesions.
- 3) Other policies
 - a. **Aetna 2013**
 - i. Covers stereotactically guided core-needle biopsy; ultrasound-guided core-needle biopsy; MRI-guided core-needle biopsy (only when the lesion cannot be visualized with mammography or ultrasonography)
- 4) Recommendation:
 - a. Advise DMAP to place CPT 19081-19086, 19281-19288 on the Diagnostic List

Systematic Review: Comparative Effectiveness of Core-Needle and Open Surgical Biopsy to Diagnose Breast Lesions

Wendy Bruening, PhD; Joann Fontanarosa, PhD; Kelley Tipton, MPH; Jonathan R. Treadwell, PhD; Jason Launder, MSc; and Karen Schoelles, MD, SM

Background: Most women undergoing breast biopsy are found not to have cancer.

Purpose: To compare the accuracy and harms of different breast biopsy methods in average-risk women suspected of having breast cancer.

Data Sources: Databases, including MEDLINE and EMBASE, searched from 1990 to September 2009.

Study Selection: Studies that compared core-needle biopsy diagnoses with open surgical diagnoses or clinical follow-up.

Data Extraction: Data were abstracted by 1 of 3 researchers and verified by the primary investigator.

Data Synthesis: 33 studies of stereotactic automated gun biopsy; 22 studies of stereotactic-guided, vacuum-assisted biopsy; 16 studies of ultrasonography-guided, automated gun biopsy; 7 studies of ultrasonography-guided, vacuum-assisted biopsy; and 5 studies of freehand automated gun biopsy met the inclusion criteria. Low-strength evidence showed that core-needle biopsies conducted under stereotactic guidance with vacuum assistance distinguished between malignant and benign lesions with an accuracy similar to

that of open surgical biopsy. Ultrasonography-guided biopsies were also very accurate. The risk for severe complications is lower with core-needle biopsy than with open surgical procedures (<1% vs. 2% to 10%). Moderate-strength evidence showed that women in whom breast cancer was initially diagnosed by core-needle biopsy were more likely than women with cancer initially diagnosed by open surgical biopsy to be treated with a single surgical procedure (random-effects odds ratio, 13.7 [95% CI, 5.5 to 34.6]).

Limitation: The strength of evidence was rated low for accuracy outcomes because the studies did not report important details required to assess the risk for bias.

Conclusion: Stereotactic- and ultrasonography-guided core-needle biopsy procedures seem to be almost as accurate as open surgical biopsy, with lower complication rates.

Primary Funding Source: Agency for Healthcare Research and Quality.

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For author affiliations, see end of text.

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www.annals.org

Breast cancer is the second most common type of cancer in women, with more than 180 000 new cases diagnosed each year in the United States (1). Women suspected of having breast cancer are usually referred for breast biopsy to determine whether the lesion is benign or malignant and whether further treatment is needed. Most women who are referred for breast biopsy do not have malignant lesions and do not require follow-up treatment (2). Biopsies may be performed by open surgery (excisional or incisional biopsy) or by minimally invasive core-needle methods. Core-needle biopsy (CNB) involves removing small samples of breast tissue through a hollow large-core needle inserted through the skin. Minimally invasive CNB has fewer complications and a shorter recovery time than open surgical biopsy. However, women and clinicians may

have concerns about the consequences of misdiagnoses based on inaccurate CNB results that could be avoided by using open surgical biopsy.

There are many different ways to perform CNB in current clinical practice. The suspicious lesion may be located by palpation or by imaging (stereotactic mammography, ultrasonography, or magnetic resonance imaging [MRI]). A device that uses vacuum suction to assist in removing tissue samples is sometimes used. Different sizes of needles may be used, and different numbers of samples may be taken. The relative accuracy of the various CNB methods, and their accuracy compared with open surgical biopsy in diagnosing suspicious breast lesions, is unclear. A sufficiently accurate method of performing minimally invasive CNB may allow many women to avoid surgery and reduce the number of surgical procedures that women with cancer undergo during treatment.

We sought to evaluate the accuracy and safety of breast biopsy methods, determine what factors may affect the accuracy of these methods, and explore their possible harms.

METHODS

The Agency for Healthcare Research and Quality commissioned this review; a technical report that describes all methods and results, including additional analyses, is published elsewhere (3). We developed and followed a

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Appendix Figure

CME quiz

Conversion of graphics into slides



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Review

Image-guided breast biopsy: state-of-the-art

E.A.M. O'Flynn*, A.R.M. Wilson, M.J. Michell

South East London Breast Screening Programme and National Breast Screening Training Centre, Kings College Hospital NHS Foundation Trust, London SE5 9RS, UK

ARTICLE INFORMATION

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Percutaneous image-guided breast biopsy is widely practised to evaluate predominantly non-palpable breast lesions. There has been steady development in percutaneous biopsy techniques. Fine-needle aspiration cytology was the original method of sampling, followed in the early 1990s by large core needle biopsy. The accuracy of both has been improved by ultrasound and stereotactic guidance. Larger bore vacuum-assisted biopsy devices became available in the late 1990s and are now commonplace in most breast units. We review the different types of breast biopsy devices currently available together with various localization techniques used, focusing on their advantages, limitations and current controversial clinical management issues.

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Introduction

Percutaneous image-guided breast biopsy has been developed largely to solve the diagnostic problem of increasing numbers of impalpable breast lesions found through breast cancer screening. The effectiveness and improvements in accuracy achieved over the last 20 years have meant that this technique is now used to assess both palpable and non-palpable lesions in both the screening and symptomatic settings.

The high accuracy of non-operative diagnosis with needle biopsy has led to a steady decline in the number of diagnostic open surgical biopsies performed over the years. From the most recent published screening data, 2616 open biopsies were performed in the UK in 2008/9 of which 69% were benign and 31% malignant. The malignant open biopsy rate has fallen from 2.04 per 1000 women in 1996/7 to 0.40 per 1000 women in 2008/9, as the non-operative diagnosis rate for cancers has increased from 63% to a substantial 95%.¹

All women with breast abnormalities are assessed using the triple diagnostic method. Clinical and imaging assessment should be carried out prior to needle biopsy. Imaging abnormalities are categorized according to a standard breast imaging reporting system. In the UK, the Royal College of Radiologists Breast Group (RCRBG) breast imaging classification is used.² This uses a five-point scale to indicate the level of suspicion for malignancy based on the imaging findings. The score can be incorporated into diagnostic protocols and provides a guide for the need for needle biopsy: Category 1 (normal) or 2 (benign findings) lesions do not require sampling. Category 3 (indeterminate/probably benign) lesions carry a low risk of malignancy 0.5–2%,^{3,4} and because of this small risk of malignancy, further investigation is indicated. The RCRBG classification system is similar to other systems (e.g. BI-RADS — Breast Imaging Reporting and Data System from the American College of Radiology), but in contrast to BI-RADS, it advocates needle biopsy for equivocal or probably benign (BI-RADS 3) findings to achieve a definitive diagnosis, rather than short-term follow-up, which has been shown to be associated with significant psychological morbidity.⁵ Percutaneous needle breast biopsy is routinely performed in centres for category 4 findings (suspicious of malignancy) and category 5 findings (highly suspicious of malignancy) lesions due to

* Guarantor and correspondent: E.A.M. O'Flynn, Department of Breast Radiology, Kings College Hospital, Denmark Hill, London, SE5 9RS, UK. Tel.: +44 2032993875; fax: 02032994363.

E-mail address: lizoflynn@doctors.org.uk (E.A.M. O'Flynn).

REVIEW

Image-Guided Methods for Biopsy of Suspicious Breast Lesions

MARIANNE J. VANDROMME, MD, HEIDI UMPHREY, MD, MS, AND HELEN KRONTRIRAS, MD*

Department of Surgery, University of Alabama at Birmingham, Birmingham, Alabama, UK

The widespread use of breast imaging has resulted in the increased detection of clinically occult suspicious breast lesions. Between 1999 and 2004 the number of breast biopsies in the United States has increased steadily. The armamentarium of methods to biopsy suspicious breast lesions has also increased significantly since the early 1990s with technological advancements for both surgical breast biopsy and percutaneous image guided breast biopsies.

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KEY WORDS: breast biopsy; core-needle biopsy; stereotactic biopsy

The widespread use of mammography, breast ultrasound, and breast magnetic resonance imaging (MRI) has resulted in the increased detection of clinically occult suspicious breast lesions. Between 1999 and 2004 the number of breast biopsies in the United States increased by 43%. Of the almost 150,000 breast biopsy procedures performed in 2004, 86% were performed with imaging guidance [1]. The armamentarium of methods to biopsy suspicious breast lesions has also increased significantly since the early 1990s with technological advancements for both surgical breast biopsy and percutaneous breast biopsy. The initial percutaneous biopsy technique to evaluate breast masses was fine-needle aspiration (FNA) with cytologic analysis and was predominantly utilized until the 1990s when core-needle biopsy (CNB) became commonplace. CNB performed with larger bore size and various imaging techniques including stereotactic (mammography), ultrasound, and MRI has become the sampling method of choice for suspicious breast lesions.

The accuracy of needle localized open-surgical biopsy is high with low-error rates (0.5%). However, the difference in sensitivity and specificity between needle localized open-surgical biopsy and image-guided percutaneous biopsy has become small with improved techniques and technology. The advantages of image-guided breast biopsies are undeniable [2]. By design image-guided percutaneous biopsy is minimally invasive, causes minimal breast deformation and scarring, is faster than open-surgical biopsy and is well tolerated by the patient. Furthermore, percutaneous biopsy can avoid time spent in the operating room, one of the most expensive locations in the hospital. Since the majority of breast lesions referred for biopsy are benign, 70–80%, image-guided biopsies yielding a concordant histological diagnosis may obviate a surgical procedure altogether [3]. In addition, patients who undergo image-guided breast biopsy of a radiologically suspicious lesion and are diagnosed with cancer generally have fewer operations [3–10]. Smith et al. [6] observed those who are diagnosed with breast cancer via image-guided biopsies have an average of 1.25 surgical procedures compared to 2.01 surgeries in women who were diagnosed via open-surgical biopsy. Image-guided breast biopsy is cost-effective when compared to open-surgical biopsy. In a review of image-guided breast biopsy, Liberman reports diagnosing indeterminate or suspicious mammographic lesions by image-guided techniques can spare open-surgical biopsy expenses and decrease the overall cost of diagnosis and treatment by 15–58% [3,11–17]. The National Comprehensive Cancer Network (NCCN), in the most recent Breast Cancer Screening and

Diagnosis Clinical Practice Guidelines, recommends percutaneous biopsy for lesions identified as a suspicious abnormality (BI-RADS 4) or highly suggestive of malignancy (BI-RADS 5) on mammographic and/or ultrasound evaluation [18]. In fact, breast program accrediting bodies including the American College of Surgeons Commission on Cancer National Accreditation Program for Breast Centers recommend percutaneous biopsy as the initial diagnostic approach and use this standard as one measure of quality when accrediting breast centers. To obtain the most accurate histological diagnosis and ultimately the best outcomes for patients, the most appropriate procedure must be determined for each patient. In this article, we will review the image-guided methods for the biopsy of suspicious breast lesions along with various sampling and localization techniques including the advantages and limitations related to each method.

SAMPLING TECHNIQUES

Fine-Needle Aspiration (FNA)

FNA was introduced as a method to biopsy suspicious palpable lesions in the 1930s, but image-guided techniques were not developed until much later [19]. In 1977, stereotactic FNA was first reported in Sweden and in 1987 ultrasound-guided FNA was first described by Fornage et al. [19–22]. The technique for obtaining the aspirate has remained unchanged since the initial description. The procedure uses a small gauge needle (18–27-G) attached to a syringe (10 or 20 ml). After the biopsy area is appropriately cleansed and anesthetized, the tip of the needle is advanced into the mass, negative pressure is applied, and cells are collected in the syringe. Agitating the needle and syringe by varying the angle of insertion and passing the needle back and forth within the lesion will dislodge cells and increase the number of cells obtained. Agitation is successful in attaining cells since breast cancer cells are believed to be less cohesive and are aspirated from the lesion more

*Correspondence to: Helen Krontriras, Department of Surgery, University of Alabama at Birmingham, Birmingham, Alabama, UK. Fax: 205-975-5970 E-mail: hkrontrir@uab.edu

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readily than normal breast cells. The aspirate is smeared onto a glass slide or submerged into a preservative solution and submitted for cytologic evaluation. At the completion of the procedure local pressure is applied to the area to prevent hematoma formation [2,23].

Overall, this technique is well tolerated by patients and can be performed quickly in most clinical settings at the time of diagnostic evaluation without the need for specialized equipment if the lesion is palpable. In some centers, FNA allows for rapid diagnosis since immediate cytology evaluation is available. FNA diagnoses breast lesions with high accuracy (72–94%), although it is skill and experience dependent [24–27]. False-positive results are uncommon if an aspirate is properly preserved. False-negative results are more common, and discordant lesions require repeat biopsy or further investigation [23]. Image-guided FNA biopsy has decreased the number of inadequate samples obtained and is more accurate with minimal additional cost [27–29].

Although FNA was the most common method of biopsying breast lesions before the 1990s, its limitations along with the advantages of CNB led to its overall decreased utilization. Many medical centers do not have a skilled cytopathologist readily available for interpretation of aspirated cells, thus making the benefit of rapid evaluation futile. Furthermore, with only cells available for analysis, the pathologist can only report if cells appear benign or malignant, and cannot distinguish between in situ or invasive carcinoma, or accurately comment on hormone receptor status [2,23,30,31]. As a result, FNA is rarely recommended as the sole biopsy technique for a routine breast lesion, but is still a valuable technique for the evaluation of axillary lymph nodes (Fig. 1) or lesions adjacent to sensitive structures, such as breast implants or posterior lesions located along the pectoralis muscle [24].

Core-Needle Biopsy

Core-needle biopsy removes intact pieces of tissue for histologic evaluation; thus revealing more structural information. It was first described by Roberts et al. [32], but only became widely practiced for evaluating breast lesions after Parker et al. [33] reported on 181 ultrasound-guided CNB in 1993. The procedure involves skin cleansing, infiltrating local anesthesia and making a small skin nick for insertion of the CNB device which is typically an 18- to 11-G spring-loaded automated needle. The needle is placed adjacent to the lesion to be biopsied since the CNB device (most are spring loaded) has an excursion that extends past the tip of the needle when deployed. The biopsy needle is fired and a small cylinder of tissue is collected. After each firing most models require the device to be withdrawn from the breast completely to collect the sample and place it in an appropriate preservative solution. Although no definitive number of core samples needed for reliable histological diagnosis has been determined, typically multiple passes must be made through the lesion to obtain adequate sampling. With each pass architectural destruction can cause local hemorrhage and sometimes may complicate obtaining quality samples. In general, solid lesions require fewer samples than lesions being biopsied for microcalcifications [34–36]. Regardless of the number of core samples taken, specimen radiology is important to verify the targeted lesion was obtained, especially if the indication for biopsy was suspicious microcalcifications seen on mammogram. Care must be taken to avoid injury to muscle, intrathoracic, or pericardial structures. After an adequate number of samples are obtained it is important to apply generous local pressure to the biopsy site.

The advantages of CNB over FNA are related to the ability to make a histologic diagnosis from cores of tissue rather than clumps of cells; hence no specialized cytopathologist is required. Even though large gauge needles are used for the biopsy, there is considerably less trauma and architectural disruption of the breast as compared to open-surgical biopsy. While the cost of CNB is greater than FNA, given the need for CNB automated device and often image guidance, it is still less costly than open-surgical biopsy.

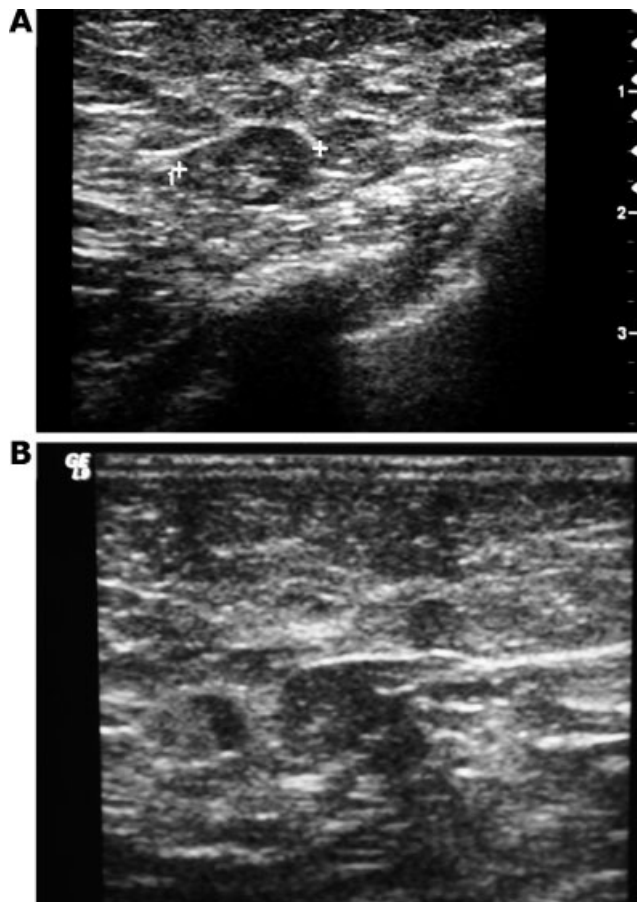
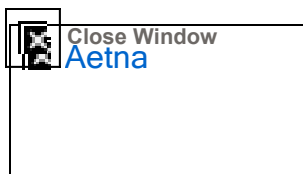


Fig. 1. **a:** US-guided axillary lymph node FNA. Grayscale US image shows an axillary lymph node with thickened cortex suspicious for malignant involvement. **b:** US-guided axillary lymph node FNA. Grayscale US image shows successful cortical sampling of the suspicious axillary lymph node with a 22-G needle.

Despite obtaining a larger sample than with FNA, a major limitation of CNB is related to the potential incomplete characterization or underestimation of disease. This commonly occurs with findings of atypical ductal hyperplasia (ADH) and ductal carcinoma in situ (DCIS), since the diagnosis can change based on the size of the sample evaluated. In a recent review, O'Flynn et al. [30] report the underestimation rate of CNB for high-risk lesions ranged from 3.4% to 100%. Further Schueller et al. [37] in a study of 1,352 14-G CNB presented an underestimation rate of 31.4% and upgraded 36.5% lesions from DCIS on biopsy to invasive cancer after surgical resection. Thus, it is recommended by the NCCN that all cases of ADH diagnosed by CNB undergo further evaluation via open-surgical biopsy to rule out DCIS or invasive carcinoma and avoid underestimation [18,38]. Additionally, the NCCN guidelines suggest that more tissue may also be necessary for diagnosis in selected cases of LCIS, mucin-producing lesions, fibroepithelial lesions or potential phyllodes tumor, papillary lesions, and radial scars.

Vacuum-Assisted Biopsy (VAC)

In the late 1990s VAC devices became available to obtain larger specimen samples and address the limitations of CNB, specifically underestimation and the difficulty in evaluating clusters of microcalcifications. The technique of VAC is similar to CNB, after skin cleansing and local anesthesia administration, a small nick is made in the skin, the



Clinical Policy Bulletin:
Breast Biopsy Procedures
Number: 0269

Policy

Aetna considers *any* of the following minimally invasive image-guided breast biopsy procedures medically necessary as alternatives to needle localization core surgical biopsy (NLBx) in members with abnormalities identified by mammography that are non-palpable or difficult to palpate (i.e., because they are deep, mobile, small (less than 2 cm), or are composed of clustered microcalcifications):

1. Advanced Breast Biopsy Instrument (ABBI); *or*
2. Stereotactically guided core-needle biopsy; *or*
3. Ultrasound-guided core-needle biopsy; *or*
4. MRI-guided core-needle biopsy; *or*
5. Vacuum assisted core-needle biopsy (Mammotome™ device).

Aetna considers other minimally invasive image-guided breast biopsy procedures (i.e., those not mentioned above) experimental and investigational (e.g., PET-guided breast biopsy [Naviscan]) because their effectiveness has not been established.

Aetna considers radioactive seed localization for breast lesion/cancer experimental and investigational because its effectiveness has not been established.

See also [CPB 0071 - Positron Emission Tomography \(PET\)](#), [CPB 0105 - Magnetic Resonance Imaging \(MRI\) of the Breast](#), and [CPB 0517 - Breast Ductal Lavage and Fiberoptic Ductoscopy](#).

Background

Policy History

▮ [Last](#)

[Review](#): 07/16/2013

Effective: 07/16/1998

Next

Review: 03/13/2014

▮ [Review History](#)

▮ [Definitions](#)

Additional Information

▮ [Clinical Policy Bulletin Notes](#)

Recent comparative studies have demonstrated several advantages of minimally invasive breast biopsy procedures over needle localization core surgical biopsy (NLBx). Minimally invasive breast biopsy procedures take less time to perform than NLBx, cause less patient discomfort and cosmetic deformity, result in less artifact on subsequent mammography, and are more cost effective. If a benign lesion is found, the patient can be followed with clinical examinations and mammography and an open surgical procedure is avoided.

Biopsies can be obtained either with a fine-needle (20-gauge) or large bore (11- and 14-gauge) needle. However, the large-core biopsy is favored over fine-needle biopsy for several reasons: (i) large core biopsy samples can be interpreted by pathologists who do not have special training in cytopathology; (ii) specimens obtained by large core biopsy are more likely to be sufficient than those obtained by fine-needle biopsy; (iii) large core biopsy samples allow the pathologist to differentiate in-situ from invasive carcinoma; and (iv) pathologists can characterize lesions more completely with large-core biopsy samples.

For larger, fixed, palpable lesions, image guidance is considered not medically necessary for performing an adequate biopsy. In these cases, palpation-guided biopsy is sufficient for locating the lesion and obtaining an adequate tissue sample. However, image-guidance has been shown to be useful for directing the biopsy of non-palpable or vaguely palpable lesions. The Center for Medicare and Medicaid Services (CMS, 2002) concluded that image-guided biopsy may be indicated for lesions that are non-palpable or vaguely palpable, and that “clinical studies suggest that such lesions may include those that are vaguely palpable, mobile, deep, or small, particularly less than 2 cm. Palpable lesions that demonstrate a small area of clustered microcalcifications on a mammogram may be difficult to biopsy using palpation alone and thus may warrant image-guided biopsy. Lesions that are difficult to biopsy using palpation are generally those that border on being non-palpable; non-palpable lesions are not amenable to palpation-guided biopsy.”

Hanna et al (2005) stated that stereotactic breast biopsy techniques minimize the surgical trauma associated with conventional wire-guided open breast biopsy for non-palpable breast lesions (NPBLs). Advanced breast biopsy instrumentation (ABBI) allows for a 2-cm core of breast tissue to be excised under stereotactic guidance in an outpatient setting. These investigators reported their initial experience with ABBI. Hospital charts from 89 ABBI procedures between October 1996 and July 2002 were retrospectively reviewed for patient characteristics, ABBI parameters, radiographic appearance, pathology, complications, and clinical follow-up. Data were presented as percentage/median (range). Median age was 59 years (range of 39 to 80 years), mammographic lesions were classified as calcifications 49 % (44/89), soft tissue 39 % (35/89), or mixed 11 % (10/89). Median radiographic

size was 7 mm (1 to 60 mm). Final pathology revealed ductal carcinoma in situ (DCIS) in 7 % (6/89) and invasive cancer in 22 % (20/89). Microscopically clear margins were obtained in 55 % (11/20) of patients with invasive cancer. Of these, 82 % (9/11) chose not to undergo further local surgical therapy. Eight patients remain disease free at 56 months (range of 41 to 95 months) follow-up. The 9th patient was deceased at 6 months from an unrelated cause. The overall complication rate was 3 % (3/89). A definitive diagnosis was obtained in 100 % of malignant and 87 % of benign cases. Median waiting time was 19 days (range of 0 to 90 days). The authors' experience demonstrated that ABBI is an effective diagnostic tool for NPBLs. It is associated with minimal complications, and provides negative margins in over 50 % of malignant cases. In selected patients with invasive cancer and negative margins, ABBI may obviate the need for further local surgical treatment. Furthermore, ABBI merits additional investigation as a therapeutic modality for early breast cancer.

Szynglarewicz et al (2011) compared the procedure duration time for different methods of minimally invasive image-guided vacuum-assisted breast biopsy (VABB). A total of 691 women with non-palpable breast masses classified as BI-RADS IV or V were studied. All of them underwent minimally invasive percutaneous VABB with an 11-gauge needle. In 402 patients an ultrasound-guided procedure with a hand-held device was performed while in 289 women stereotactic biopsy was carried out using a dedicated prone table unit with digital imaging. In each case the duration of biopsy was measured in terms of the total procedure time, room time and physician time. There were no significant differences between the stereotactic and ultrasound-guided groups with regard to patient age, body mass index, menopausal status, history of parity, hormone replacement therapy, breast parenchymal pattern (according to Wolfe's classification), family history of breast cancer, mass size and number of samples. Ultrasound-guided biopsy was found to take significantly less time than prone stereotactic biopsy in every aspect of procedure duration. Mean total procedure time, room time, and physician time in minutes were 26.7 ± 8.2 versus 47.5 ± 9.4 ($p < 0.01$), 23.1 ± 8.5 versus 36.5 ± 9.2 ($p < 0.05$), and 12.3 ± 5.6 versus 18.6 ± 5.9 ($p < 0.05$), respectively. The authors concluded that ultrasound-guided breast biopsy is less time-consuming than the stereotactic procedure for both the patient and the physician. Because of the shorter procedure time (as well as other well-known advantages: real-time imaging, lower cost), ultrasound-guided biopsy should be considered the method of choice for sampling suspicious nonpalpable breast masses.

Radioactive seed localization (RSL) has also been advocated as a means to facilitate the operative excision of non-palpable breast lesions, and appears to be a new option for women undergoing lumpectomies. With this procedure, a radiologist places a very low-energy radioactive seed into the abnormal tissue or tumor, guided by mammography. During

the surgery, the surgeon uses a hand-held Geiger counter to more precisely identify the location of the tumor. The Geiger counter also allows the surgeon to obtain a 3-D view of the tumor's location. On the day of the lumpectomy, the patient arrives about 2 hours before the surgery to receive light sedation and a local anesthetic to numb the surgical area. After the surgeon removes the abnormal tissue or tumor along with the radioactive seed, the incision is closed and bandaged. Once the seed is removed with the breast tissue, the radioactivity is gone. The patient is able to leave the hospital later that same day.

Rao et al (2010) stated that seed localization uses a radioactive source to identify non-palpable breast lesions for excision; it is an emerging alternative to wire-localized breast biopsy (WLBB). Previous single health system studies reported decreased rates of re-excision and improved patient convenience with this technique. This study was the first to implement this procedure in a public health care delivery system composed of a primarily minority and low-income population. A multi-disciplinary team was formed to create a protocol for RSL and monitor the results. After 50 RSL were successfully completed, a retrospective matched-pair analysis with patients who had undergone WLBB during the same period was performed. Overall experience with the RSL protocol was reviewed, along with the occurrence of a seed loss. Processes necessary to re-activate the RSL protocol and prevent future losses were delineated. Radioactive seed localization is associated with decreased rates of re-excision and can be successfully implemented in a public health care system. The authors concluded that RSL is an attractive alternative to WLBB in a high-volume, county-based population. It allows increased efficiency in the operating room and has a low rate of complications. Cautionary measures must be taken to ensure proper seed chain of custody to prevent seed loss.

Jakub et al (2010) noted that WLBB remains the standard method for the surgical excision of non-palpable breast lesions. Because of many of its shortcomings, most important a high microscopic positive margin rate, alternative approaches have been described, including RSL. These investigators highlighted the literature regarding RSL, including safety, the ease of the procedure, billing, and oncologic outcomes. Medline and PubMed were searched using the terms "radioactive seed" and "breast". All peer-reviewed studies were included in this review. The authors concluded that RSL is a promising approach for the resection of non-palpable breast lesions. It is a reliable and safe alternative to WLBB. Radioactive seed localization is at least equivalent compared with WLBB in terms of the ease of the procedure, removing the target lesion, the volume of breast tissue excised, obtaining negative margins, avoiding a second operative intervention, and allowing for simultaneous axillary staging.

McGhan et al (2011) performed a retrospective review of all consecutive RSL procedures performed at a single institution from

January 2003 through October 2010. A total of 1,000 RSL breast procedures were performed in 978 patients. Indications for RSL included invasive carcinoma (52 %), in-situ carcinoma (22 %), atypical hyperplasia (11 %), and suspicious percutaneous biopsy findings (15 %). A total of 1,148 seeds were deployed using image guidance, with 76 % placed greater than or equal to 1 day before surgery. Most procedures (86 %) utilized 1 seed. A negative margin was achieved at the first operation in 97 % of patients with invasive carcinoma and 97 % of patients with ductal carcinoma in-situ (DCIS). An additional 9 % of patients with invasive carcinoma and 19 % of patients with DCIS had close (less than or equal to 2 mm) margins, and underwent re-excision. Sentinel lymph node biopsy was successfully performed in 99.8 % of cases. Adverse events included 3 seeds (0.3 %) not deployed correctly on first attempt and 30 seeds (2.6 %) displaced from the breast specimen during excision of the targeted lesion. All seeds were successfully retrieved, with no radiation safety concerns. Local recurrence rates were 0.9 % for invasive breast cancer and 3 % for DCIS after mean follow-up of 33 months. There was no evidence of a learning curve. The authors concluded that RSL is a safe, effective procedure that is easy to learn, with a low incidence of positive/close margins. They stated that RSL should be considered as the method of choice for localization of non-palpable breast lesions. The main drawback of this study was its retrospective, non-randomized design.

Lovrics et al (2011) examined if radio-guided localization surgery (RGL) (radio-guided occult lesion localization [ROLL] and RSL) for non-palpable breast cancer lesions produces lower positive margin rates than standard WLBB surgery. These researchers performed a comprehensive literature review to identify clinical studies using either ROLL or RSL; included studies examined invasive or in-situ breast cancer, and reported pathologically assessed margin status or specimen volume/weight. Two reviewers independently assessed study eligibility and quality and abstracted relevant data on patient and surgical outcomes. Quantitative data analyses were performed. A total of 52 clinical studies on ROLL (n = 46) and RSL (n = 6) were identified; 27 met inclusion criteria: 12 studies compared RGL to WLBB and 15 studies were single cohorts using RGL. A total of 10 studies were included in the quantitative analyses. Data for margin status and re-operation rates from 4 randomized controlled trials (RCT; n = 238) and 6 cohort studies were combined giving a combined odds ratio (OR) of 0.367 and 95 % confidence interval (CI): 0.277 to 0.487 (p < 0.001) for margins status and OR 0.347, 95 % CI: 0.250 to 0.481 (p < 0.001) for re-operation rates. The authors concluded that the findings of this systematic review of RGL versus WLBB demonstrated that RGL technique produces lower positive margins rates and fewer re-operations. While this review was limited by the small size and quality of RCTs, the odds ratios suggested that RGL may be a superior technique to guide surgical resection of non-palpable breast cancers.

They stated that these results should be confirmed by larger, multi-centered RCTs.

Langhans et al (2012) stated that the Danish national mammography screening program leads to identification of an increased number of small non-palpable breast tumors, suitable for breast-conserving surgery. Accurate lesion localization is therefore important. The current standard is WLBB and although effective it involves a risk of high rates of positive margin and re-operations. New methods are emerging and RSL seems promising with regards to re-operation rates and logistics. In RSL, a small titanium seed containing radioactive iodine is used to mark the lesion.

The National Comprehensive Cancer Network (NCCN, 2012) clinical practice guideline on breast cancer does not mention the use of RSL.

CPT Codes / HCPCS Codes / ICD-9 Codes

CPT codes covered if selection criteria are met:

19102

19103

+19295

76645

76942

77031

CPT codes not covered for indications listed in the CPB:

Radioactive seed localization:

No specific code

Other CPT codes related to the CPB:

10021

10022

19100

19101

19296

+19297

19298

76098

77002

77011

77012

77021

77032

+ 77051 -

77059

Other ICD-9 codes related to the CPB:

174.0 - 175.9 Malignant neoplasm of breast

198.2 Secondary malignant neoplasm of skin of breast

198.81 Secondary malignant neoplasm of breast

217 Benign neoplasm of breast

233.0 Carcinoma in situ of breast

238.3 Neoplasm of uncertain behavior of breast

610.0 - 610.8 Benign mammary dysplasias

611.72 Lump or mass in breast

793.80 - Nonspecific abnormal findings on radiological
793.89 examination (mammogram) of the breast [breast
nodules]

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Genetic Tests

Genetic Testing

- 1) DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis (CPT 81161)
 - a. Currently, CPT 81408, which includes full gene sequencing for Duchenne/Becker muscular dystrophy is covered on the Diagnostic List
 - b. Guidelines
 - i. **Abbs 2010**, best practices guideline
 1. Genetic testing is required to confirm diagnosis, and therapy may be directed based on type of mutation present
 2. Recommend for prenatal diagnosis for male fetuses only
 3. Since whole exon deletions are the predominant type of mutation in the DMD gene (approx.. 65%), an initial screen which detects the majority of deletions should be the minimum level of diagnostic test offered
 - c. Other policies
 - i. **Premara BCBS 2013**
 1. Covers 81161 for men with signs and symptoms of a dystrophinopathy in order to confirm the diagnosis and direct treatment, for at-risk female relative to confirm or exclude the need for cardiac surveillance, and for preconception testing to determine the likelihood of an affected offspring in a woman considering a pregnancy
 - d. Recommendation: Diagnostic List
- 2) MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme), methylation analysis (CPT 81287)
 - a. MGMT is a major predictive factor for treatment response to alkylating agents including temozolomide (TMZ) of glioblastoma multiforme (GBM) patient
 - b. Literature
 - i. **Jenson 2010**, review of molecular diagnostic testing for gliomas
 1. Recently, the use of *MGMT* methylation status in anaplastic (ie, WHO grade III) gliomas was evaluated in the Neuro-Oncology Working Group of the German Cancer Society NOA-04 trial and the European Organisation for Research and Treatment of Cancer (EORTC) 26951 trial. In both trials, *MGMT* methylation status conferred prognostic benefit but did not specifically predict response to therapy with alkylating drugs.
 2. Recently, patients whose glioblastomas have methylation of the *MGMT* gene promoter have been reported to have a greater likelihood of a radiographic pseudoprogression when treated with temozolomide than do patients whose tumours do not have such methylation. During pseudoprogression, the neuro imaging profile seems to worsen after temozolomide,

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Genetic Tests

but then improves with continued therapy. Thus, another role for testing for *MGMT* promoter methylation could be evaluation of the likelihood of pseudoprogression

3. Recommendation: Given that temozolomide and radiation therapy remain the standard of care for all patients with glioblastoma, regardless of *MGMT* promoter methylation status, upfront diagnostic testing is not necessary. Nonetheless, the methylation status of the *MGMT* promoter provides prognostic information that many patients and oncologists will wish to have.

ii. **Yip 2008**, review of molecular diagnostic testing for malignant gliomas

1. *MGMT* testing is not typically undertaken for prognostic purposes.
2. predictive testing for *MGMT* is also not ready for routine clinical implementation at the present time. Although the data have demonstrated differences in significance between the survival benefits conferred by temozolomide in patients whose glioblastomas have *MGMT* methylation versus those whose tumors lack *MGMT* methylation, there was a trend that nearly achieved significance ($p = 0.06$) for temozolomide benefit in patients whose tumors lacked methylation. Given that temozolomide is a well-tolerated oral agent and the only agent in the last 2 decades to show a definite survival benefit, it seems highly unlikely that temozolomide would be withheld from a patient whose glioblastoma lacked *MGMT* promoter methylation. One can argue that negative testing might enable a decision to stop temozolomide therapy in a patient whose tumor demonstrated radiologic progression during therapy, but that same decision might be reached as well on the basis of clinical and radiologic data. Therefore, it seems unlikely that *MGMT* promoter methylation assays will play an important predictive role until the time that an alternative chemotherapy to temozolomide exists.

c. Recommendation: Excluded List

- i. Will need to modify non-prenatal genetic testing guideline to include this exclusion
- 3) Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores (CPT 81504)
 - a. Testing to attempt to identify tissue of origin for cancers of unknown primary (CUP)

i. **NCCN 2012 guideline**

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1. "The panel currently feels that data are insufficient to confirm that molecular profiling should be used routinely in the diagnostic workup of patients with CUP."
- b. Recommendation: Excluded List
 - i. Will need to modify non-prenatal genetic testing guideline to include this exclusion

DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE

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

- A) Related to genetic testing for patients with breast/ovarian and colon/endometrial cancer 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 and endometrial cancer) services (CPT 81292-81300, 81317-81319) and familial adenomatous polyposis (FAP) services (CPT 81201-81203) should be provided as defined by the NCCN Clinical Practice Guidelines in Oncology. Colorectal Cancer Screening. V. 1.2013 2-2012 (4/27/12 5/13/13). www.nccn.org
 - b) BRCA1/BRCA2 testing services (CPT 81211-81217) for women without a personal history of breast and/or ovarian cancer should be provided to high risk women as defined in [GuideLineRef.,3] or as otherwise defined by the US Preventive Services Task Force.
 - c) BRCA1/BRCA2 testing services (CPT 81211-81217) for women with a personal history of breast and/or ovarian cancer 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. V.1.2011 (4/7/11). www.nccn.org
 - d) PTEN (Cowden syndrome) services (CPT 81321-81323) should be provided as defined by the NCCN Clinical Practice Guidelines in Oncology. Colorectal Screening. V. 1.2013 2-2012 (4/27/12 5/13/13). www.nccn.org.
 - 2) Genetic counseling should precede genetic testing for hereditary cancer. Very rarely, it may be appropriate for a genetic test to be performed prior to genetic counseling for a patient with cancer. If this is done, genetic counseling should be provided as soon as practical.
 - a) Pre and post-test genetic counseling by the following providers should be covered.
 - i) Medical Geneticist (M.D.) - Board Certified or Active Candidate Status from the American Board of Medical Genetics
 - ii) Clinical Geneticist (Ph.D.) - Board Certified or Active Candidate Status from the American Board of Medical Genetics.
 - iii) Genetic Counselor - Board Certified or Active Candidate Status from the American Board of Genetic Counseling, or Board Certified by the American Board of Medical Genetics.
 - iv) Advance Practice Nurse in Genetics - Credential from the Genetic Nursing Credentialing Commission.
 - 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

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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.
- B) 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. In 2012, this test may also be billed using one of CPT 88384-88386, or stacking CPTs 83890-83915.
 - 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. In 2012, this test may also be billed using one of CPT 88384-88386, or stacking CPTs 83890-83915.
 - 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.
- C) 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)

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- 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 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 for the Non-Prenatal Genetic Testing Algorithm AND the specified situations:
- a) CPT 81205, BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, Maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X): Cover only when the newborn screening test is abnormal and serum amino acids are normal
 - b) Diagnostic testing for cystic fibrosis (CF)
 - i) CFTR, cystic fibrosis transmembrane conductance regulator tests. CPT 81220, 81223, 81222: For infants with a positive newborn screen for cystic fibrosis or who are symptomatic for cystic fibrosis, or for clients that have previously been diagnosed with cystic fibrosis but have not had genetic testing, CFTR gene analysis of a panel containing at least the mutations recommended by the American College of Medical Genetics* (CPT 81220) is covered. If two mutations are not identified, CFTR full gene sequencing (CPT 81223) is covered. If two mutations are still not identified, duplication/deletion testing (CPT 81222) is covered. These tests may be ordered as reflex testing on the same specimen.
 - c) Carrier testing for cystic fibrosis
 - i) CFTR gene analysis of a panel containing at least the mutations recommended by the American College of Medical Genetics* (CPT 81220) is covered.
 - d) 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 thromboembolism; 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.
 - e) 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 thromboembolism; 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 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.
 - g) CPT 81332 SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z): The alpha-1-antitrypsin protein level

2014 CPT Code Review Issues

Genetic Tests

should be the first line test of a suspected diagnosis of AAT deficiency in symptomatic individuals with unexplained liver disease or obstructive lung disease that is not asthma or in a middle age individual with unexplained dyspnea. Generic testing or the alpha-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.

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



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Workshop report

Best Practice Guidelines on molecular diagnostics in Duchenne/Becker muscular dystrophies

Stephen Abbs^{a,*}, Sylvie Tuffery-Giraud^b, Egbert Bakker^c, Alessandra Ferlini^d, Thomas Sejersen^e, Clemens R. Mueller^f^a DNA Laboratory, GSTS Pathology, Guy's Hospital, London SE1 9RT, UK^b Université Montpellier1, UFR Médecine and INSERM U827, Montpellier F-34000, France^c Department of Human and Clinical Genetics, LUMC, 2333 AL Leiden, The Netherlands^d Sezione di Genetica Medica, Dipartimento di Medicina Sperimentale e Diagnostica Università di Ferrara, Italy^e Karolinska Institute, Neuropediatric Unit, Stockholm 17176, Sweden^f Universität Würzburg, Institut für Humangenetik, Biozentrum, 97074 Würzburg, Germany

1. Introduction

A meeting of 29 senior scientists from Europe, the USA, India and Australia, was held in Naarden, The Netherlands on November 14–16, 2008, to establish consensus Best Practice Guidelines for molecular diagnosis of Duchenne and Becker muscular dystrophy (DMD/BMD). New therapeutic trials for DMD demand accurate diagnosis of the disorder, especially where the therapy is targeted towards specific mutations. These guidelines aim to help diagnostic laboratories attain that accuracy by describing the minimum standards for acceptable molecular diagnostic testing of DMD. For the different types of clinical referral received by a molecular diagnostic laboratory, the guidelines recommend the appropriate tests to be carried out, interpretation of the results and how those results should be reported.

2. Internal and external quality control

All laboratories offering molecular genetic testing for DMD/BMD must follow established good laboratory practice, as documented for example in *Guidelines for Quality Assurance in Molecular Genetic Testing*, published by the Organisation for Economic Co-operation and Development [1].

In addition to following such guidelines, a laboratory should ideally demonstrate that it complies with internationally recognised standards for laboratory testing (e.g. ISO standards 15189: 2007 *Medical laboratories – Particular requirements for quality and competence*), by achieving formal accreditation with a member organisation of the International Laboratory Accreditation Cooperation (ILAC) or equivalent national accreditation body.

All tests should be validated/verified in individual laboratories prior to implementation; it is not acceptable to rely on the validation of a test by another laboratory, since that does not guarantee

that it will perform accurately and reliably in all labs. A series of control samples representing all mutation types should therefore be collected by each laboratory to facilitate test validation/verification, and exchange of samples between laboratories is encouraged to allow this. External quality assessment schemes provide further validation of testing procedures and methods, and laboratories should participate in appropriate EQA schemes for DMD testing. If this is not possible, inter-laboratory exchange of samples should be arranged to compare and validate test results.

3. Types of laboratory referral

Patient samples are referred to clinical molecular genetic laboratories for the following investigations:

3.1. Diagnosis in male patients

Affected males suspected to have a dystrophinopathy based on high serum creatine kinase (CK) levels and/or muscle biopsy, are referred for a molecular confirmation of the clinical diagnosis (see Fig. 1). Molecular confirmation of a dystrophinopathy is achieved by demonstrating the presence of a clearly pathogenic variant in the *DMD* gene. Absence of a *DMD* mutation would reduce the likelihood of a patient having a dystrophinopathy, with the reduction being dependent on the sensitivity of the mutation screening procedure(s) used. It is currently not possible to refute a diagnosis of a dystrophinopathy based on the results of genetic testing, since no mutation detection protocol which is currently available can demonstrate 100% sensitivity.

From the patients' and relatives' perspectives, the speed with which a diagnosis can be made is extremely important in order to minimize anxiety and to reduce the risk of recurrence of the disease in the family. Therefore, in some instances a muscle biopsy and dystrophin analysis by immunohistochemistry might be needed to establish a quick and definite diagnosis.

Appropriate genetic counselling in the family is dependent on the knowledge of the diagnosis in the patient. This should be borne in mind when determining the appropriate procedures

* Corresponding author.

E-mail addresses: stephen.abbs@gsts.com (S. Abbs), sylvie.tuffery@inserm.fr (S. Tuffery-Giraud), e.bakker@lumc.nl (E. Bakker), fla@unife.it (A. Ferlini), thomas.sejersen@ki.se (T. Sejersen), crm@biozentrum.uni-wuerzburg.de (C.R. Mueller).



MEDICAL POLICY

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Genetic Testing for Duchenne and Becker Muscular Dystrophy

Number 12.04.86

Effective Date May 28, 2013

Revision Date(s) N/A

Replaces N/A

Policy

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Genetic testing for *DMD* gene mutations may be considered **medically necessary** under the following conditions:

- In a male with signs and symptoms of a dystrophinopathy in order to confirm the diagnosis and direct treatment.
- For at-risk female relatives: (see [Policy Guidelines](#) and [Benefit Application](#))
 - To confirm or exclude the need for cardiac surveillance
- For preconception testing to determine the likelihood of an affected offspring in a woman considering a pregnancy

Related Policies

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[12.04.91](#)

[General Approach to Genetic Testing](#)

Policy Guidelines

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Heterozygous females are at increased risk for cardiomyopathy and need routine cardiac surveillance and treatment.

At-risk females are defined as first- and second-degree female relatives and include the proband's mother, female siblings of the proband, female offspring of the proband, the proband's maternal grandmother, maternal aunts, and their offspring.

Effective in 2013, there are CPT codes applicable to this testing:

81161 DMD (dystrophin) (e.g., Duchenne/Becker muscular dystrophy) deletion analysis and duplication analysis, if performed

81408 includes DMD (dystrophin) (e.g., Duchenne/Becker muscular dystrophy), full gene sequence

Description

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Description

Mutations in the *DMD* gene, which encodes the protein dystrophin, may result in a spectrum of X-linked muscle diseases. The severe end of the spectrum includes the progressive muscle diseases Duchenne and Becker muscular dystrophy and dilated cardiomyopathy. Genetic testing can confirm a diagnosis of a dystrophinopathy and distinguish the less and more severe forms, as well as identify female carriers at risk.

Background

The dystrophinopathies include a spectrum of muscle diseases. The mild end of the spectrum includes asymptomatic increases in serum concentration of creatine phosphokinase and clinical symptoms such as muscle cramps with myoglobinuria and/or isolated quadriceps myopathy. The severe end of the spectrum includes progressive muscle diseases that lead to substantial morbidity and mortality. When skeletal muscle is primarily affected, they are classified as Duchenne or Becker muscular dystrophy and when the heart is primarily affected, as *DMD*-associated dilated cardiomyopathy (left ventricular dilation and heart failure).

Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD), the most common muscular dystrophy, is a severe childhood X-linked recessive disorder that results in significant disability due to skeletal myopathy and cardiomyopathy. The disease is characterized by progressive, symmetric muscle weakness and gait disturbance resulting from a defective dystrophin gene. (1) The incidence of DMD is estimated to be 1 in 3,500 newborn male births, (2) and approximately one-third of DMD cases arise from new mutations and have no known family history. (1) Infant males with DMD are often asymptomatic. Manifestations may be present as early as the first year of life in some patients, but clinical manifestations most often appear during preschool from years 2 to 5. Affected children present with gait problems, calf hypertrophy, positive Gower's sign, and difficulty climbing stairs. The affected child's motor status may plateau between 3 and 6 years of life with deterioration beginning at 6 to 8 years. The majority of patients will be wheelchair bound by ages 9 to 12 years but will retain preserved upper-limb function until a later period. Cardiomyopathy occurs after 18 years of age. Late complications are cardiorespiratory (e.g. decreased pulmonary function as a result of respiratory muscle weakness and cardiomyopathy). These severe complications commonly appear in the second decade of life and eventually lead to death. (1) Few individuals with DMD survive beyond the third decade.

Becker Muscular Dystrophy

Becker muscular dystrophy (BMD) is characterized by later-onset skeletal muscle weakness. Individuals remain ambulatory into their 20s. Despite the milder skeletal muscle involvement, heart failure from cardiomyopathy is a common cause of morbidity and the most common cause of death in these patients, with a mean age of death in the mid-40s.

Female Carriers

Females heterozygous for a *DMD* mutation can manifest symptoms of the disease. (3) An estimated 2.5% to 7.8% of female carriers are manifesting carriers who develop symptoms ranging from a mild muscle weakness to a rapidly progressive DMD-like muscular dystrophy. (4) Female carriers are at increased risk for dilated cardiomyopathy. Most heterozygous women do not show severe myopathic features of DMD, possibly due to compensation by a normal X chromosome with inactivation of the mutated *DMD* gene in the affected X chromosome. (5) In some cases, this compensation can be reversed by a non-random or skewed inactivation of X chromosome resulting in greater expression of the affected X chromosome and some degree of myopathic features. (6) Other mechanisms of manifesting female carriers include X chromosome rearrangement involving the *DMD* gene and complete or partial absence of the X chromosome (Turner syndrome). (3)

Clinical diagnosis

DMD

The suspicion of DMD should be considered irrespective of family history, and is most commonly triggered by an observation of abnormal muscle function in a male child, the detection of an increase in serum creatine kinase tested for unrelated indications, or after the discovery of increased serum transaminases (aspartate aminotransferase and alanine aminotransferases). Clinical examination by a neuromuscular specialist for DMD includes visual inspection of mechanical function such as running, jumping, climbing stairs and getting up from the floor. Common presenting symptoms include abnormal gait with frequent falls, difficulties in rising from the floor or in tip-toe walking, and pseudo hypertrophy of the calves. A clinical examination may reveal decreased or lost muscle reflexes and commonly a positive Gower sign. An elevation of serum creatine kinase, at least 10-20 times normal levels (between 5,000 and 150,000 IU/L), is non-specific to DMD but is always present in affected patients. (1) Electromyography and nerve-conduction were traditional parts of the assessment of neuromuscular disorders, but now these tests are no longer believed to be necessary for the specific assessment of DMD. (7) An open skeletal muscle biopsy is needed when a negative test for deletions or duplications to the *DMD* gene is negative. The biopsy will provide general signs of muscular dystrophy including muscle fiber degeneration, muscle regeneration, and increased content of connective tissue and fat. Dystrophin analysis on a muscle biopsy will always be abnormal in affected patients but is not specific to DMD.

BMD

Becker muscular dystrophy (BMD) has a clinical picture similar to DMD but is milder than DMD and has a later onset. BMD presents with progressive symmetric muscle weakness, often with calf hypertrophy, although weakness of quadriceps femoris may be the only sign. Activity-induced cramping may be present in some individuals, and flexion contractures of the elbows may be present late in the course. Neck flexor muscle strength is preserved, which differentiates BMD from DMD. Serum creatine kinase shows moderate-to-severe elevation (5-100 times the normal level).

Molecular diagnosis

DMD is the only gene in which mutations are known to cause DMD, BMD and DMD-associated cardiomyopathy. Molecular genetic testing of *DMD* can establish the diagnosis of a dystrophinopathy without muscle biopsy in most patients with DMD and BMD.

The dystrophinopathies are X-linked recessive and penetrance is complete in males.

The gene that codes for dystrophin is the largest known human gene. (1) A molecular confirmation of DMD and BMD is achieved by confirming the presence of a pathogenic variant in this gene by a number of available assays. The large size of the dystrophin gene results in a complex mutational spectrum with over 5,000 different reported mutations, as well as a high spontaneous mutation rate. (8)

Treatment of Duchenne Muscular Dystrophy

There is no cure for Duchenne or Becker muscular dystrophy, and treatment is aimed at control of symptoms to improve quality of life. However, the natural history of the disease can be changed by several strategies such as corticosteroid therapy, proper nutrition or rehabilitative interventions. Glucocorticoids can slow the loss of muscle strength and may be started when a child is diagnosed or when muscle strength begins to decline. (7) The goal of this therapy is to preserve ambulation and minimize later respiratory, cardiac, and orthopedic complications. Glucocorticoids work by decreasing inflammation, preventing fibrosis, improving muscle regeneration, improving mitochondrial function, decreasing oxidative radicals, and stopping abnormal apoptosis pathways. (1) Bone density measurement and immunization are prerequisites for corticosteroid therapy initiation, which typically begins at 2 to 5 years of age although there has been no demonstrated benefit of earlier therapy, before 5 years of age. (1)

New therapeutic trials require accurate diagnoses of these disorders, especially when the therapy is targeted toward specific mutations. (9) Several of these therapies are currently undergoing clinical trials with two of the most promising being anti-sense oligonucleotide induced exon-skipping and gene repair and replacement with an adeno-associated viral (AAV) vector. (10) Exon-skipping is a molecular therapy aimed at skipping the transcription of a targeted exon to restore a correct reading frame using antisense oligonucleotides. The result is a DMD protein that is formed without the mutated exon and a normal, non-shifted reading frame. Exon skipping may be able to restore DMD protein function so that the treated patient's phenotypic expression more closely resembles BMD. Gene transfer using AAV vector therapy involves the transfer of a functional *DMD* gene to the patient using this nonpathogenic and low immune response vector. (11)

Regulatory Status

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were found. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing

Scope

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Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply.

Benefit Application

[\[TOP\]](#)

N/A

Rationale

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Literature Review

This policy was created in February 2013, with a review of the literature through MEDLINE as of January 3, 2013.

Analytic validity (refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent)

- Deletions of one or more exons account for 60-70% of mutations in individuals with DMD and BMD. (12)
- Duplications account for 5-10% of mutations in DMD and BMD. (12)

Multiplex PCR may be used to amplify exons known to be most frequently deleted in DMD-affected patients. Results obtained from testing two polymerase chain reaction (PCR) multiplex sets suggest a detection rate of approximately 98% with this methodology. (13, 14) Multiplex PCR is the most widely available testing choice but is only able to detect deletions. In addition, this method does not cover the whole gene, so a deletion might not always be fully characterized. (7) An alternative to multiplex PCR is the use of a quantitative assay (e.g. multiplex ligation-dependent probe amplification or comparative genomic hybridization [also called chromosomal microarray or CMA]) of all exons. These methods have the advantage of being able to detect whole exon deletions, as well as duplications.

Point mutations (small deletions or insertions, single-base changes, and splicing mutations) account for approximately 25-35% of mutations in males with DMD and about 10-20% of males with BMD.

If deletion/duplication detection is negative, then dystrophin gene sequencing should be done to look for point mutations or small deletions/insertions. (7)

Sequencing of the entire *DMD* gene to detect point mutations can be performed by traditional PCR and Sanger sequencing, or by more automated methods such as universal long PCR combined with massive pyrosequencing.

There is a lack of published studies in the peer-review literature that evaluate analytic validity. According to information from the website of a large reference laboratory, deletion/duplication analysis by CMA and point mutations by full gene sequencing detects 98-99% of mutations in both males and females. (15)

Certain types of assays may cause false-positive results if the method identifies an apparent single-exon deletion or duplication based on the absence or increased amplification, respectively, of a single PCR amplification, or hybridization; when this occurs, the result must be confirmed using an alternative assay. This different assay will verify whether the initial result could have been caused by a sequence variant preventing hybridization of a primer, probe, etc., or for duplications, if the result was an anomaly. Therefore, false positives are expected to be infrequent.

Clinical validity (refers to the diagnostic performance of the test—sensitivity, specificity, positive and negative predictive values). Virtually all males with DMD/BMD have identifiable DMD mutations, indicating a high clinical sensitivity for genetic testing. In males with DMD and BMD, phenotypes are best correlated with the degree of expression of dystrophin, largely determined by the reading frame of the spliced message obtained from the deleted allele.

A reading frame is the way in which a messenger RNA sequence of nucleotides can be read as a series of base triplets, and affects which protein is made. In DMD, the function of the dystrophin protein is completely lost due to mutations that disrupt the reading frame. Therefore, prematurely truncated, unstable dystrophins are generated. In contrast, patients with BMD have low levels of full-length dystrophin or carry in-frame mutations that allow for the generation of partially functional proteins. This so-called reading frame rule explains the phenotypic differences between DMD and BMD patients. Since this rule was postulated in 1988, (16) thousands of mutations have been reported for DMD and BMD, of which an estimated 90% fit this rule. (17)

Testing strategy

To establish the diagnosis of a proband with DMD or BMD in a male with clinical findings that suggest a dystrophinopathy:

- Perform DMD genetic testing for deletion/duplication analysis first.
- If a mutation is not identified, perform sequence analysis for a point mutation.
- If a disease-causing DMD mutation is identified, the diagnosis of a dystrophinopathy is established.
- In cases where a distinction between DMD and BMD is difficult, the reading frame "rule" states that the type of deletion/duplication (those that alter the reading frame [out-of-frame], which correlates with the more severe phenotype of DMD versus those that do not alter the reading frame [in-frame] which correlate with the milder BMD phenotype) can distinguish the DMD and BMD phenotypes with 91-92% accuracy.
- If no disease-causing DMD mutation is identified, skeletal muscle biopsy is warranted for western blot and immunohistochemistry studies of dystrophin.

For carrier testing in at-risk female relatives:

- When the proband's DMD mutation is known, test for that deletion/duplication or point mutation using appropriate testing method.
- When an affected male is not available for testing, perform testing by deletion/duplication first and if no mutation is identified, by sequence analysis.

The evaluation of relatives at risk includes females who are the sisters or maternal female relatives of an affected male and females who are a first-degree relative of a known or possible carrier female.

Clinical utility (how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes)

The clinical utility of testing for *DMD* gene mutations for the index case includes:

- Establishing the diagnosis and initiating/directing treatment of the disease, such as glucocorticoids, evaluation by a cardiologist, avoidance of certain agents (e.g. botulinum toxin injections), and prevention of secondary complications (immunizations, reducing risk of fractures).
- Distinguishing between DMD and BMD.
- Avoidance of a muscle biopsy in the majority of cases.

The clinical utility of testing for *DMD* gene mutations for at-risk female relatives includes

- Testing to identify heterozygous females to confirm or exclude the need for cardiac surveillance.
- Preconception testing in a woman considering offspring who would alter reproductive decision-making based on test results.

Summary

The analytic and clinical validity of genetic testing for Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are high. *DMD* is the only gene in which mutations cause the dystrophinopathies, and molecular genetic testing can establish the diagnosis in most patients. Nearly all affected individuals will be found to have a *DMD* mutation, and false positives are expected to be rare.

The clinical utility of *DMD* gene testing can be established for the index case and for at-risk female relatives. For the index case, utility lies in confirmation of the diagnosis without a muscle biopsy, initiation of effective treatment, and in distinguishing between DMD and the less severe BMD. For at-risk female relatives, the test can confirm or exclude the need to undergo routine cardiac surveillance, and can indicate the likelihood of an affected offspring in women considering children.

Therefore, genetic testing for *DMD* gene mutations may be considered medically necessary to establish a diagnosis in a male with clinical signs and symptoms suggestive of a dystrophinopathy and as testing for at-risk female relatives.

Practice Guidelines and Position Statements

A meeting of 29 senior scientists from Europe, the US, India, and Australia established consensus Best Practice Guidelines for the molecular diagnosis of DMD/BMD. The recommendations for testing are, if there is a clinical suspicion of a dystrophinopathy, first screen for deletions and duplications. If no deletion or duplication is detected, but the clinical diagnosis is verified, screening for point mutations should be performed. (9)

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Coding

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Codes	Number	Description
CPT	81161	DMD (dystrophin) (e.g., Duchenne/Becker muscular dystrophy) deletion analysis and duplication analysis, if performed
	81408	Molecular pathology procedure, Level 9 (e.g., analysis of >50 exons in a single gene by DNA sequence analysis) --includes DMD (dystrophin) (e.g., Duchenne/Becker muscular dystrophy), full gene sequence

ICD-9-CM Diagnosis	359.1	Hereditary progressive muscular dystrophy (includes Duchenne muscular dystrophy)
	783.9	Other symptoms concerning nutrition, metabolism, and development (includes dystrophy NOS)
	V26.31	Testing of female genetic disease carrier status
ICD-10-CM (effective 10/01/14)	G71.0	Muscular dystrophy
	R62.59	
	Z31.430	
ICD-10-PCS (effective 10/01/14)		Not applicable. ICD-10-PCS codes are only used for inpatient services.

Appendix

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N/A

History

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Date	Reason
05/28/13	New policy. Policy created with literature search through January 3, 2013. Medically necessary to establish a diagnosis in a male with clinical signs and symptoms suggestive of a dystrophinopathy and in at-risk female relatives.

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Molecular pathology in adult gliomas: diagnostic, prognostic, and predictive markers

Michael Jansen, Stephen Yip, David N Louis

Over the past 10 years, there has been an increasing use of molecular markers in the assessment and management of adult malignant gliomas. Some molecular signatures are used diagnostically to help pathologists classify tumours, whereas others are used to estimate prognosis for patients. Most crucial, however, are those markers that are used to predict response to certain therapies, thereby directing clinicians to a particular treatment while avoiding other potentially deleterious therapies. Recently, large-scale genome-wide surveys have been used to identify new biomarkers that have been rapidly developed as diagnostic and prognostic tools. Given these developments, the pace of discovery of new molecular assays will quicken to facilitate personalised medicine in the setting of malignant glioma.

Introduction

Primary tumours of the CNS account for about 2% of human malignancies. The most common CNS tumours in adults are malignant gliomas. In general, malignant gliomas are not curable tumours, but their management has undergone change over the past two decades, with novel approaches to surgery, radiation, and chemotherapy that have improved survival and quality of life for patients to variable degrees. In this Review, we outline how new molecular diagnostic advances have also had a role in changing the management of patients with malignant gliomas over the past 20 years.

Until recently, treatment decisions regarding malignant gliomas began with establishing diagnosis by standard histopathology only. Histopathology has been a dynamic tool for nearly 100 years, providing knowledge about the biology and behaviour of many neoplasms. The 2007 WHO classification,¹ the most recent consensus approach to CNS tumour diagnosis, divides the malignant gliomas of adults into astrocytic tumours—the most malignant of which is termed glioblastoma—and oligodendrogliomas and oligo-astrocytomas. The data gained from histopathological examination of tumour tissue have been augmented, but not displaced, by molecular approaches to tissue diagnosis.

Knowledge about the molecular biology of cancer, including CNS tumours, continues to increase. Having a dynamic classification of tumours enables the integration of newly discovered markers to help determine prognosis and likelihood of therapeutic response. We focus on the markers that are used in the evaluation of adult malignant gliomas, specifically 1p/19q co-deletion, methylation of the O-6 methylguanine-DNA methyltransferase (MGMT) gene promoter, alterations in the epidermal growth factor receptor (EGFR) pathway, and isocitrate dehydrogenase 1 (IDH1) gene mutations. Molecular approaches are also used in the assessment of other CNS tumours of neuroepithelial origin, notably in paediatric tumours such as medulloblastoma,² atypical teratoid/rhabdoid tumour,³ and potentially in pilocytic astrocytoma.⁴

1p/19q loss

Background

After empirical observations of favourable responses to chemotherapy in a high proportion of recurrent anaplastic oligodendrogliomas (a grade III tumour), Cairncross and colleagues⁵ documented that such oligodendrogliomas with loss of the short arm of chromosome 1 (1p) were preferentially chemosensitive when treated with a procarbazine, lomustine, and vincristine chemotherapy regimen. Moreover, patients whose tumours had co-deletions of 1p and the long arm of chromosome 19 (19q) had substantially improved survival times. These findings have been replicated many times over the past 10 years, and the correlations with therapeutic sensitivity have been extended to other drugs such as temozolomide^{6,7} and procedures such as radiotherapy.⁸ Such data suggest that this marker is more useful as an indicator of tumour vulnerability to a broad range of therapeutic options than as a specific predictor of chemosensitivity. As a result, assessment of 1p and 19q status has been widely implemented in the neuro-oncological management of patients with anaplastic oligodendroglioma.⁹

The frequency of 1p/19q co-deletion has been estimated to be 80–90% in grade II oligodendrogliomas and 50–70% in grade III oligodendrogliomas.¹⁰ Notably, however, although the 1p and 19q regions have been extensively mapped and many genes have been evaluated as candidate tumour suppressor genes, no tumorigenic genes have been definitively implicated. In most cases, deletions seem to represent complete chromosomal arm loss, which might be the result of an unbalanced centromeric translocation of 1p and 19q.^{11,12} Although the genes on 1p and 19q remain unidentified, many correlations have been made regarding 1p/19q loss. For example, tumours with 1p/19q co-deletion frequently show classic histology^{13–15} and commonly have IDH1 and IDH2 mutations.¹⁶ Anaplastic oligodendrogliomas with 1p/19q co-deletions preferentially have a proneural gene expression profile.¹⁷ This profile, which is partly characterised by expression of neuronal genes, is over-represented among low-grade gliomas and might predict therapeutic response in glioblastoma.¹⁸ However, 1p and

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Pathology Service (M Jansen MBBCh, S Yip MD, Prof D N Louis MD) and Cancer Center (D N Louis), Massachusetts General Hospital, Boston, MA, USA; Department of Pathology, Harvard Medical School, Boston, MA, USA (D N Louis); Histopathology Department, Cork University Hospital, Wilton, Cork, Ireland (M Jansen); and Department of Pathology and Laboratory Medicine and Centre for Translational and Applied Genomics, British Columbia Cancer Agency, Vancouver, Canada (S Yip)

Correspondence to: Prof David N Louis, James Homer Wright Pathology Laboratories, Massachusetts General Hospital, 55 Fruit Street, Warren 225, Boston, MA 02114, USA
dlouis@partners.org

REVIEW ARTICLE

Molecular Diagnostic Testing in Malignant Gliomas: A Practical Update on Predictive Markers

Stephen Yip, MD, PhD, A. John Iafrate, MD, PhD, and David N. Louis, MD

Abstract

Advances in understanding the molecular underpinnings of cancer and in molecular diagnostic technologies have changed the clinical practice of oncologic pathology. The development of targeted therapies against specific molecular alterations in cancer further portends changes in the role of the pathology laboratory to guide such custom therapies. To reconcile the flood of scientific discoveries in this area, the promises of highly touted novel therapeutics, and the practicality of applying this knowledge to the day-to-day practice of clinical neuropathology, the present review highlights the operative differences between diagnostic, predictive, and prognostic markers, and discusses issues surrounding the transition of prospective biomarkers to routine laboratory implementation. This review focuses on 3 predictive molecular markers that are either in clinical use or are contemplated for use in the evaluation of malignant gliomas: assessment of 1p/19q loss in oligodendroglial tumors, examination of O₆-methylguanine DNA methyltransferase promoter methylation status in glioblastomas, and molecular dissection of the epidermal growth factor receptor–phosphatidylinositol 3-kinase pathway in glioblastomas. Implementation of such predictive markers is not straightforward and requires critical review of the available literature and attention to practical laboratory, compliance, financial, and clinical management issues.

Key Words: Biomarkers, Glioblastoma, Glioma, Molecular diagnostics, Neuropathology, Oligodendroglioma.

INTRODUCTION

Advances in understanding the molecular basis of disease and identification of disease biomarkers have heralded the era of molecular diagnostics in pathology. This development, however, comes with unique sets of challenges that will confront the pathologist. Indeed, the pathologist will be essential to evaluate scientific evidence critically and to determine whether a candidate molecular marker can provide information to alter disease management. The

pathologist will also have to consider the practicality of adopting a new test in the clinical setting. Such considerations are now typically undertaken under increasing pressure from clinicians to incorporate testing for newly discovered markers. In this regard, the pathologist must balance the desire to bring the latest research findings to the bedside with the need to observe numerous checks and balances that ensure that newly incorporated markers are ready for clinical testing.

NOVEL MARKERS: BASIC CONSIDERATIONS

Biomarkers are important diagnostics tools in oncology; they also aid in monitoring disease progression and assist in determining prognosis and predicting therapeutic response (1, 2). Biomarkers vary from specific proteins and antigens to unique genetic, epigenetic, and proteomic profiles, but common to all markers is that they provide information specific to a disease process. They function to supplement, and rarely to supplant, the histopathologic examination of tissues that is the mainstay of traditional oncologic pathology.

Diagnostic, Prognostic, and/or Predictive

Before the laboratory implementation of a novel biomarker, there must be a clear definition of whether its use lies in the diagnostic, prognostic, or predictive realm. A diagnostic marker aids in the initial recognition of cancer or its relapse (3). A prognostic marker presents information pertaining to the natural history of disease and, therefore, the probability of disease relapse and durability of remission. A predictive marker identifies probability of response to a specific therapeutic agent or modality (4). Differentiating between these different types of markers is important so that one can make informed clinical decisions (5, 6). A single marker, however, may provide various combinations of diagnostic, prognostic, and predictive information. For example, expression of the estrogen receptor by immunohistochemistry is relevant in the diagnostic workup of metastatic lesions suspicious to be derived from a breast carcinoma primary, but it is also relevant to survival (prognostic) and potential response to hormonal interventional therapies (predictive) (7).

The clinical use of a potential marker is based on the magnitude of its diagnostic, prognostic, or predictive abilities and on the reliability of such changes. The former reflects the degree of clinical benefit that results from

From the James Homer Wright Pathology Laboratories (SY, AJI, DNL), Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts.

Send correspondence and reprint requests to: David N. Louis, MD, James Homer Wright Pathology Laboratories, Massachusetts General Hospital, 55 Fruit Street, Warren 2, Boston, MA 02114; E-mail: dlouis@partners.org

2014 CPT Code Review Issues

Procedures

Percutaneous transcatheter septal reduction therapy (eg, **alcohol septal ablation**) including temporary pacemaker (CPT 93583)

- 1) Description: a percutaneous, minimally-invasive treatment performed by an interventional cardiologist to relieve symptoms and improve functional status in severely symptomatic patients with hypertrophic cardiomyopathy. The alternative is an open procedure to surgically reduce the septal size.
- 2) Studies cite a procedure related mortality between 0.5-2%. Complete heart block requiring the insertion of a pacemaker occurs in approximately 10% of cases
- 3) Literature
 - a. **Gersh 2011**, ACCH/AHA consensus guideline for treatment of hypertrophic cardiomyopathy
 - i. When surgery is contraindicated or the risk is considered unacceptable because of serious comorbidities or advanced age, alcohol septal ablation, when performed in experienced centers, can be beneficial in eligible adult patients with HCM with LVOT obstruction and severe drug-refractory symptoms (usually NYHA functional classes III or IV) (*Level of Evidence: B*)
 - ii. Alcohol septal ablation, when performed in experienced centers, may be considered as an alternative to surgical myectomy for eligible adult patients with HCM with severe drug-refractory symptoms and LVOT obstruction when, after a balanced and thorough discussion, the patient expresses a preference for septal ablation. (*Level of Evidence: B*)
 - iii. The effectiveness of alcohol septal ablation is uncertain in patients with HCM with marked (ie, >30 mm) septal hypertrophy, and therefore the procedure is generally discouraged in such patients. (*Level of Evidence: C*)
 - iv. Septal reduction therapy should not be done for adult patients with HCM who are asymptomatic with normal exercise tolerance or whose symptoms are controlled or minimized on optimal medical therapy. (*Level of Evidence: C*)
 - v. Septal reduction therapy should not be done unless performed as part of a program dedicated to the longitudinal and multidisciplinary care of patients with HCM. (*Level of Evidence: C*)
 - vi. Alcohol septal ablation should not be done in patients with HCM with concomitant disease that independently warrants surgical correction (eg, coronary artery bypass grafting for CAD, mitral valve repair for ruptured chordae) in whom surgical myectomy can be performed as part of the operation. (*Level of Evidence: C*)
 - vii. Alcohol septal ablation should not be done in patients with HCM who are less than 21 years of age and is discouraged in adults less than 40 years of age if myectomy is a viable option. (*Level of Evidence: C*)
 - b. **NICE 2004**

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Procedures

- i. Current evidence on the safety and efficacy of non-surgical reduction of the myocardial septum appears adequate to support the use of the procedure
 - ii. Non-surgical reduction of the myocardial septum does not require open chest surgery or cardiopulmonary bypass. It involves inserting a catheter into the femoral artery and passing it up into the heart under X-ray control. Alcohol is injected into an artery that supplies blood to the septum. This destroys a part of the muscle in the septum, which then becomes thinner.
- c. Other policies
- i. **Aetna 2012:** Aetna considers percutaneous transluminal septal myocardial ablation (PTSMA) by alcohol-induced septal branch occlusion medically necessary for hypertrophic obstructive cardiomyopathy (HOCM) in adults when all of the following criteria are met:
 - 1. Member has severe symptoms (e.g., dyspnea, angina pectoris, [pre]syncope, palpitations or heart failure) for at least 6 months despite optimal drug therapy (e.g., beta-blockers, calcium-antagonists), dual chamber pacing therapy and/or ineffective previous surgical myotomy/myectomy; *and*
 - 2. Member is classified as New York Heart Association class III or IV (see below); *and*
 - 3. Member has a classical, asymmetric subaortic HOCM identified by echocardiography, and not a mid-ventricular, a concealed membranous subaortic stenosis, nor supravalvular form; *and*
 - 4. Echocardiography shows left ventricular wall thickness of greater than 13 mm in adults in the absence of another cause for left ventricular hypertrophy; 15 mm in an athlete; *and*
 - 5. Member has systolic anterior motion of the mitral valve on echocardiography; *and*
 - 6. Member has a resting left ventricular outflow tract (LVOT) gradient of greater than 30 mm Hg or a stressed gradient of greater than 60 mm Hg, or member has less severe symptoms and LVOT of greater than 50 mm Hg at rest or greater than 100 mm Hg under stress; *and*
 - 7. Member does not have coronary artery disease that would preclude performance of the procedure.
 - ii. **Anthem BCBS 2012:** Alcohol septal ablation is considered **medically necessary** as a treatment of hypertrophic cardiomyopathy (HCM) in adults (age 21 and older) when all of the following criteria are met:
 - 1. Severe heart failure symptoms (New York Heart Association [NYHA] class III or IV) or other exertional symptoms (such as syncope or near syncope) refractory to drug therapy; **and**

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2. Left ventricular outflow tract (LVOT) gradient greater than or equal to 50 mm Hg at rest or with physiological provocation, including but not limited to: exercise, valsalva maneuver or amyl nitrate

4) Recommendation:

- a. Add 93583 to line 109 CARDIOMYOPATHY, HYPERTROPHIC MUSCLE
- b. Add the following guideline to line 109

GUIDELINE NOTE XXX ALCOHOL SEPTAL ABLATION

Line 109

Alcohol septal ablation (CPT 93583) is included on line 109 only for adult patients with hypertrophic cardiomyopathy when all of the following conditions are met:

- 1) Severe heart failure symptoms (New York Heart Association [NYHA] class III or IV)
- 2) Severe symptoms refractory to optimal medical management
- 3) LVOT obstruction is present
- 4) Surgery is contraindicated or has unacceptable risk due to serious comorbidities or advanced age.
- 5) No concomitant disease is present that independently warrants surgical correction in whom surgical myectomy can be performed as part of the operation.
- 6) The ablation is performed at an experienced center

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Procedures

Mechanical **chest wall oscillation** to facilitate lung function (CPT 94669)

- 1) Definition: Chest wall oscillation involves using devices/systems for clearing excess mucus from lung airways (bronchi and bronchioles). It is principally used in the treatment of cystic fibrosis, but is gaining use in the treatment of other diseases, such as bronchiectasis, COPD, cerebral palsy and muscular dystrophy, in which excessive mucus can block airways due to excessive production or impaired clearance.
- 2) Current Prioritized List:
 - a. E0483 High frequency chest wall oscillation air-pulse generator system—Ancillary
 - b. 99467-99468 (Manipulation chest wall, such as cupping, percussing, and vibration to facilitate lung function) are on lines 11, 14, 65, 78, 213, 233, 236, 248, 306, 490.
- 3) Literature
 - a. **Morrison 2011**, Cochrane review of chest oscillation devices for cystic fibrosis (CF)
 - i. N=34 studies (total of 859 participants)
 - ii. One long-term study (seven months) compared oscillatory devices with either conventional physiotherapy or breathing techniques and found statistically significant differences in some lung function parameters in favour of oscillating devices.
 - iii. **Authors' conclusions** There was no clear evidence that oscillation was a more or less effective intervention overall than other forms of physiotherapy. More adequately-powered long-term randomised controlled trials are necessary.
 - b. **Dosman 2005**, review of chest oscillation
 - i. Conclusions: current opinion suggests that high frequency chest oscillation (HFCC) increases mucolysis, mucus transport, and pulmonary function in patients with cystic fibrosis, while improving their quality of life. It appears to be an adequate alternative to other mucus clearance modalities. HFCC is now also being used to enhance mucus clearance in children with developmental disorders involving neuromuscular dysfunction.
 - c. **British Thoracic Society 2013**, guideline for treatment of children with neuromuscular weakness
 - i. Oscillatory techniques such as high-frequency chest wall oscillation and intrapulmonary percussive ventilation should be considered in children who have difficulty mobilising secretions or who have persistent atelectasis, despite use of other airway clearance techniques. [level of Evidence D]
- 4) Other policies
 - a. **CMS 2013**

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Procedures

- i. High frequency chest wall oscillation devices (HFCWO) (E0483) are covered for beneficiaries who meet one of criterion 1, 2 or 3 AND criterion 4
 - 1. There is a diagnosis of cystic fibrosis (ICD-9 277.00, 277.02).
 - 2. There is a diagnosis of bronchiectasis (ICD-9 011.50-011.56, 494.0, 494.1, 748.61) which has been confirmed by a high resolution, spiral, or standard CT scan and which is characterized by:
 - a. Daily productive cough for at least 6 continuous months; or
 - b. Frequent (i.e., more than 2/year) exacerbations requiring antibiotic therapy.
 - c. Chronic bronchitis and chronic obstructive pulmonary disease (COPD) in the absence of a confirmed diagnosis of bronchiectasis do not meet this criterion.
 - 3. The beneficiary has one of the following neuromuscular disease diagnoses:
 - Post-polio (138)
 - Acid maltase deficiency (277.6)
 - Anterior horn cell diseases (335.0-335.9)
 - Multiple sclerosis (340)
 - Quadriplegia (344.00-344.09)
 - Hereditary muscular dystrophy (359.0, 359.1)
 - Myotonic disorders (359.21-359.29)
 - Other myopathies (359.4, 359.5, 359.6, 359.89)
 - Paralysis of the diaphragm (519.4)
 - 4. There must be well-documented failure of standard treatments to adequately mobilize retained secretions.

b. Aetna 2013

- i. Aetna considers high-frequency chest compression systems (e.g., the Freuencer, the SmartVest, the MedPulse Respiratory Vest System, the Vest Airway Clearance System, the ABI Vest, Respin11 Bronchial Clearance System, and the InCourage Vest/System) medically necessary in lieu of chest physiotherapy for the following indications, where there is a documented failure of standard treatments to adequately mobilize retained secretions:
 - 1. Bronchiectasis, confirmed by CT scan, characterized by daily productive cough for at least 6 continuous months or by frequent (i.e., more than 2 times/year) exacerbations requiring antibiotic therapy; *or*
 - 2. Cystic fibrosis; *or*
 - 3. The member has one of the following neuromuscular disease diagnoses:
 - a. Acid maltase deficiency

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- b. Anterior horn cell diseases
 - c. Hereditary muscular dystrophy
 - d. Multiple sclerosis
 - e. Myotonic disorders
 - f. Other myopathies
 - g. Paralysis of the diaphragm
 - h. Post-polio
 - i. Quadriplegia.
- 4. Lung transplant recipients, within the first 6 months post-operatively, who are unable to tolerate standard chest physiotherapy.
 - ii. Aetna considers high-frequency chest compression systems experimental and investigational for other indications (e.g., alpha 1-antitrypsin deficiency, cerebral palsy, coma, kyphosis, leukodystrophy, scoliosis, and stiff-person (stiff-man) syndrome; not an all inclusive list) because their effectiveness for these indications has not been established.
- 5) Recommendation: add high frequency chest oscillation (CPT 94669) to the following lines:
 - a. **26** CYSTIC FIBROSIS
 - b. **65** BRONCHIECTASIS
 - c. **78** NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES

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Procedures

Low frequency, non-contact, non-thermal ultrasound, including topical application(s), when performed, wound assessment (CPT 97610)

- 1) Definition: Noncontact, low-frequency ultrasound is a technology intended to remove necrotic tissue from chronic wounds (debridement) and to stimulate closure of non-healing wounds.
- 2) Literature
 - a. **Cullum 2011**, Cochrane review of ultrasound therapy for chronic leg ulcers
 - i. N=8 trials were included; all had unclear, or high, risks of bias
 - ii. 6 trials evaluated high frequency ultrasound
 1. Significantly more patients healed with US than without it at 7 - 8 weeks (pooled RR 1.4, 95% CI 1.0 to 1.96), but later assessments at 12 weeks showed the increased risk of healing with US was no longer statistically significant (pooled RR 1.47, 95% CI 0.99 to 2.20).
 - iii. 2 RCTs evaluated low frequency US
 1. Both trials reported no evidence of a difference in the proportion of ulcers healed with US compared with no US
 - iv. Conclusions: The trials evaluating US for venous leg ulcers are small, poor-quality and heterogeneous. There is no reliable evidence that US hastens healing of venous ulcers. There is a small amount of weak evidence of increased healing with US, but this requires confirmation in larger, high-quality RCTs. There is no evidence of a benefit associated with low frequency US.
 - b. **Voight 2011**, meta-analysis of ultrasound for chronic wound healing
 - i. N=8 RCTs
 - ii. Results demonstrated that early healing (at ≤ 5 months) in patients with venous stasis and diabetic foot ulcers was favorably influenced by both high- and low-intensity ultrasound delivered at a low frequency—either via contact or noncontact techniques.
 - iii. However, the quality of the data may be suspect, especially for low-frequency low-intensity noncontact ultrasound because of significant biases.
- 3) Other policies
 - a. **BCBS 2013**
 - i. Use of low-frequency, non-contact, non-thermal, ultrasound therapy is considered **investigational and not medically necessary** for all applications.
- 4) Recommendation: Excluded List

2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: Executive Summary: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Writing Committee Members, Bernard J. Gersh, Barry J. Maron, Robert O. Bonow, Joseph A. Dearani, Michael A. Fifer, Mark S. Link, Srihari S. Naidu, Rick A. Nishimura, Steve R. Ommen, Harry Rakowski, Christine E. Seidman, Jeffrey A. Towbin, James E. Udelson and Clyde W. Yancy

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2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: Executive Summary

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Developed in Collaboration With the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons

WRITING COMMITTEE MEMBERS*

Bernard J. Gersh, MB, ChB, DPhil, FACC, FAHA, Co-Chair*†; Barry J. Maron, MD, FACC, Co-Chair*†; Robert O. Bonow, MD, MACC, FAHA‡; Joseph A. Dearani, MD, FACC§||; Michael A. Fifer, MD, FACC, FAHA*†; Mark S. Link, MD, FACC, FHRS*¶; Srihari S. Naidu, MD, FACC, FSCAI*#; Rick A. Nishimura, MD, FACC, FAHA†; Steve R. Ommen, MD, FACC, FAHA†; Harry Rakowski, MD, FACC, FASE†**; Christine E. Seidman, MD, FAHA†; Jeffrey A. Towbin, MD, FACC, FAHA†; James E. Udelson, MD, FACC, FASNC‡§§; Clyde W. Yancy, MD, FACC, FAHA|||

*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply; see Appendix 1 for detailed information.

†ACCF/AHA Representative.

‡ACCF/AHA Task Force on Performance Measures Liaison.

§Society of Thoracic Surgeons Representative.

||American Association for Thoracic Surgery Representative.

¶Heart Rhythm Society Representative.

#Society for Cardiovascular Angiography and Interventions Representative.

**American Society of Echocardiography Representative.

††Pediatric Content Expert.

‡‡Heart Failure Society of America Representative.

§§American Society of Nuclear Cardiology Representative.

|||ACCF/AHA Task Force on Practice Guidelines Liaison.

¶¶Former Task Force member during this writing effort.

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ACCF/AHA TASK FORCE MEMBERS

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Preamble

It is essential that the medical profession play a central role in critically evaluating the evidence related to drugs, devices, and procedures for the detection, management, or prevention of disease. Properly applied, rigorous, expert analysis of the available data documenting absolute and relative benefits and risks of these therapies and procedures can improve the effectiveness of care, optimize patient outcomes, and favorably affect the cost of care by focusing resources on the most effective strategies. One important use of such data is the production of clinical practice guidelines that, in turn, can provide a foundation for a variety of other applications such as performance measures, appropriateness use criteria, clinical decision support tools, and quality improvement tools.

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) have jointly engaged in the production of guidelines in the area of cardiovascular disease since 1980. The ACCF/AHA Task Force on Practice Guidelines (Task Force) is charged with developing, updating, and revising practice guidelines for cardiovascular diseases and procedures, and the Task Force directs and oversees this effort. Writing committees are charged with assessing the evidence as an independent group of authors to develop, update, or revise recommendations for clinical practice.

Experts in the subject under consideration have been selected from both organizations to examine subject-specific data and write guidelines in partnership with representatives from other medical practitioner and specialty groups. Writing committees are specifically charged to perform a formal literature review, weigh the strength of evidence for or against particular tests, treatments, or procedures, and include estimates of expected health outcomes where data exist. Patient-specific modifiers, comorbidities, and issues of patient preference that may influence the choice of tests or therapies are considered. When available, information from studies on cost is considered, but data on efficacy and clinical

outcomes constitute the primary basis for recommendations in these guidelines.

In analyzing the data and developing the recommendations and supporting text, the writing committee used evidence-based methodologies developed by the Task Force, which are described elsewhere.¹ The committee reviewed and ranked evidence supporting current recommendations with the weight of evidence ranked as Level A if the data were derived from multiple randomized clinical trials (RCTs) or meta-analyses. The committee ranked available evidence as Level B when data were derived from a single RCT or nonrandomized studies. Evidence was ranked as Level C when the primary source of the recommendation was consensus opinion, case studies, or standard of care. In the narrative portions of these guidelines, evidence is generally presented in chronological order of development. Studies are identified as observational, retrospective, prospective, or randomized when appropriate. For certain conditions for which inadequate data are available, recommendations are based on expert consensus and clinical experience and ranked as Level C. An example is the use of penicillin for pneumococcal pneumonia, for which there are no RCTs and treatment is based on clinical experience. When recommendations at Level C are supported by historical clinical data, appropriate references (including clinical reviews) are cited if available. For issues where sparse data are available, a survey of current practice among the clinicians on the writing committee was the basis for Level C recommendations and no references are cited. The schema for Classification of Recommendations and Level of Evidence is summarized in Table 1, which also illustrates how the grading system provides an estimate of the size and the certainty of the treatment effect. A new addition to the ACCF/AHA methodology is separation of the Class III recommendations to delineate whether the recommendation is determined to be of “no benefit” or associated with “harm” to the patient. In addition, in view of the increasing number of comparative effectiveness studies, comparator verbs and suggested phrases for writing recommendations for the comparative effectiveness of one treatment/strategy with respect to another for Class of Recommendation I and IIa, Level of Evidence A or B only have been added.

The Task Force makes every effort to avoid actual, potential, or perceived conflicts of interest that may arise as a result of relationships with industry and other entities (RWI) among the writing committee. Specifically, all members of the writing committee, as well as peer reviewers of the document, are required to disclose all relevant relationships and those 12 months prior to initiation of the writing effort. The policies and procedures for RWI for this guideline were those in effect at the initial meeting of this committee (March 28, 2009), which included 50% of the writing committee with no relevant RWI. All guideline recommendations require a confidential vote by the writing committee and must be approved by a consensus of the members voting. Members who were recused from voting are indicated on the title page of this document with detailed information included in Appendix 1. Members must recuse themselves from voting on any recommendations where their RWI apply. If a writing committee member develops a new RWI during his/her

Table 1. Applying Classification of Recommendation and Level of Evidence

		SIZE OF TREATMENT EFFECT										
		CLASS I <i>Benefit >>> Risk</i> Procedure/Treatment SHOULD be performed/ administered	CLASS IIa <i>Benefit >> Risk</i> Additional studies with focused objectives needed IT IS REASONABLE to per- form procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> Additional studies with broad objectives needed; additional registry data would be helpful Procedure/Treatment MAY BE CONSIDERED	CLASS III <i>No Benefit</i> or CLASS III <i>Harm</i> <table><tr><th colspan="2">Procedure/ Test</th><th>Treatment</th></tr><tr><td>COR III: No benefit</td><td>Not Helpful</td><td>No Proven Benefit</td></tr><tr><td>COR III: Harm</td><td>Excess Cost w/o Benefit or Harmful</td><td>Harmful to Patients</td></tr></table>	Procedure/ Test		Treatment	COR III: No benefit	Not Helpful	No Proven Benefit	COR III: Harm
Procedure/ Test		Treatment										
COR III: No benefit	Not Helpful	No Proven Benefit										
COR III: Harm	Excess Cost w/o Benefit or Harmful	Harmful to Patients										
ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses							
	LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies							
	LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care							
Suggested phrases for writing recommendations		should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit is not recommended is not indicated should not be performed/ administered/ other is not useful/ beneficial/ effective	COR III: Harm potentially harmful causes harm associated with excess morbidity/mortality should not be performed/ administered/ other						
Comparative effectiveness phrases†		treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B									

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

tenure, he/she is required to notify guideline staff in writing. These statements are reviewed by the Task Force and all members during each conference call and/or meeting of the writing committee and are updated as changes occur. For detailed information regarding guideline policies and procedures, please refer to the ACCF/AHA methodology and policies manual.¹ RWI pertinent to this guideline for authors and peer reviewers are disclosed in Appendixes 1 and 2, respectively. Comprehensive disclosure information for the Task Force is also available online at <http://www.cardiosource.org/ACC/About-ACC/Leadership/Guidelines-and-Documents-Task-Forces.aspx>. The work of the writing

committee was supported exclusively by the ACCF and AHA without commercial support. Writing committee members volunteered their time for this effort.

The ACCF/AHA practice guidelines address patient populations (and healthcare providers) residing in North America. As such, drugs that are currently unavailable in North America are discussed in the text without a specific class of recommendation. For studies performed in large numbers of subjects outside of North America, each writing group reviews the potential impact of different practice patterns and patient populations on the treatment effect and on the relevance to the ACCF/AHA target population to deter-

mine whether the findings should inform a specific recommendation.

The ACCF/AHA practice guidelines are intended to assist healthcare providers in clinical decision making by describing a range of generally acceptable approaches for the diagnosis, management, and prevention of specific diseases or conditions. These practice guidelines represent a consensus of expert opinion after a thorough review of the available current scientific evidence and are intended to improve patient care. The guidelines attempt to define practices that meet the needs of most patients in most circumstances. The ultimate judgment regarding care of a particular patient must be made by the healthcare provider and patient in light of all the circumstances presented by that patient. Thus, there are situations in which deviations from these guidelines may be appropriate. Clinical decision making should consider the quality and availability of expertise in the area where care is provided. When these guidelines are used as the basis for regulatory or payer decisions, the goal should be improvement in quality of care. The Task Force recognizes that situations arise for which additional data are needed to better inform patient care; these areas will be identified within each respective guideline when appropriate.

Prescribed courses of treatment in accordance with these recommendations are effective only if they are followed. Because lack of patient understanding and adherence may adversely affect outcomes, physicians and other healthcare providers should make every effort to engage the patient's active participation in prescribed medical regimens and lifestyles.

The guideline will be reviewed annually by the Task Force and considered current unless it is updated, revised, or withdrawn from distribution. The full-text version^{1a} of the guideline is e-published in the *Journal of the American College of Cardiology* and *Circulation* and is posted on the ACC (www.cardiosource.org) and AHA (my.americanheart.org) World Wide Web sites. Guidelines are official policy of both the ACCF and AHA.

Alice K. Jacobs, MD, FACC, FAHA
Chair, ACCF/AHA Task Force on Practice Guidelines

1. Introduction

1.1. Methodology and Evidence Review

The recommendations listed in this document are, whenever possible, evidence based. An extensive evidence review was conducted through January 2011. Searches were limited to studies, reviews, and other evidence conducted in human subjects and published in English. Key search words included, but were not limited to, *hypertrophic cardiomyopathy (HCM)*, *surgical myectomy*, *ablation*, *exercise*, *sudden cardiac death (SCD)*, *athletes*, *dual-chamber pacing*, *left ventricular outflow tract (LVOT) obstruction*, *alcohol septal ablation*, *automobile driving* and *implantable cardioverter-defibrillators (ICDs)*, *catheter ablation*, *defibrillators*, *genetics*, *genotype*, *medical management*, *magnetic resonance imaging*, *pacing*, *permanent pacing*, *phenotype*, *pregnancy*, *risk stratification*, *sudden death in athletes*, *surgical septal myectomy*, and *septal reduction*. References selected and

published in this document are representative and not all-inclusive.

1.2. Organization of the Writing Committee

The committee was composed of physicians and cardiac surgeons with expertise in HCM, invasive cardiology, non-invasive testing and imaging, pediatric cardiology, electrophysiology, and genetics. The committee included representatives from the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons.

1.3. Document Review and Approval

This document was reviewed by 2 outside reviewers nominated by both the ACCF and AHA, as well as 2 reviewers each from the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons. Other content reviewers included members from the ACCF Adult Congenital and Pediatric Cardiology Council, ACCF Surgeons' Scientific Council, and ACCF Interventional Scientific Council. All information on reviewers' RWI was distributed to the writing committee and is published in this document (Appendix 2).

This document was approved for publication by the governing bodies of the ACCF and the AHA and endorsed by the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons.

1.4. Scope of the Guideline

Although there are reports of this disease dating back to the 1800s, the first modern pathologic description was provided over 50 years ago by Teare² and the most important early clinical report by Braunwald et al in 1964.³

The impetus for the guidelines is based on an appreciation of the frequency of this clinical entity and a realization that many aspects of clinical management, including the use of diagnostic modalities and genetic testing, lack consensus. Moreover, the emergence of 2 different approaches to septal reduction therapy (septal myectomy and alcohol septal ablation) in addition to the ICD has created considerable controversy. The discussion and recommendations about the various diagnostic modalities apply to patients with established HCM and to a variable extent to patients with a high index of suspicion of the disease.

Although the Task Force was aware of the lack of high levels of evidence regarding HCM provided by clinical trials, it was believed that a guideline document based on expert consensus that outlines the most important diagnostic and management strategies would be helpful.

To facilitate ease of use, it was decided that recommendations in the pediatric and adolescent age groups would not

appear as a separate section but instead would be integrated into the overall content of the guideline where relevant.

2. Recommendations for HCM

2.1. Genetic Testing Strategies/Family Screening—Recommendations

Class I

1. Evaluation of familial inheritance and genetic counseling is recommended as part of the assessment of patients with HCM.^{4–9} (*Level of Evidence: B*)
2. Patients who undergo genetic testing should also undergo counseling by someone knowledgeable in the genetics of cardiovascular disease so that results and their clinical significance can be appropriately reviewed with the patient.^{10–14} (*Level of Evidence: B*)
3. Screening (clinical, with or without genetic testing) is recommended in first-degree relatives of patients with HCM.^{4–7,9,15,16} (*Level of Evidence: B*)
4. Genetic testing for HCM and other genetic causes of unexplained cardiac hypertrophy is recommended in patients with an atypical clinical presentation of HCM or when another genetic condition is suspected to be the cause.^{17–19} (*Level of Evidence: B*)

Class IIa

1. Genetic testing is reasonable in the index patient to facilitate the identification of first-degree family members at risk for developing HCM.^{5,8,15} (*Level of Evidence: B*)

Class IIb

1. The usefulness of genetic testing in the assessment of risk of SCD in HCM is uncertain.^{20,21} (*Level of Evidence: B*)

Class III: No Benefit

1. Genetic testing is not indicated in relatives when the index patient does not have a definitive pathogenic mutation.^{4–9,22} (*Level of Evidence: B*)
2. Ongoing clinical screening is not indicated in genotype-negative relatives in families with HCM.^{22–25} (*Level of Evidence: B*)

See Data Supplement 1 for additional data regarding genetic testing strategies/family screening.

2.1.1. Genotype-Positive/Phenotype-Negative Patients—Recommendation

Class I

1. In individuals with pathogenic mutations who do not express the HCM phenotype, it is recommended to perform serial electrocardiogram (ECG), transthoracic echocardiogram (TTE), and clinical assessment at periodic intervals (12 to 18 months in children and adolescents and about every 5 years in adults), based on the patient's age and change in clinical status.^{26–29} (*Level of Evidence: B*)

2.2. Electrocardiography—Recommendations

Class I

1. A 12-lead ECG is recommended in the initial evaluation of patients with HCM. (*Level of Evidence: C*)
2. Twenty-four-hour ambulatory (Holter) electrocardiographic monitoring is recommended in the initial evaluation of patients with HCM to detect ventricular tachycardia (VT) and identify patients who may be candidates for ICD therapy.^{30–33} (*Level of Evidence: B*)
3. Twenty-four-hour ambulatory (Holter) electrocardiographic monitoring or event recording is recommended in patients with HCM who develop palpitations or lightheadedness.^{30–32} (*Level of Evidence: B*)
4. A repeat ECG is recommended for patients with HCM when there is worsening of symptoms. (*Level of Evidence: C*)
5. A 12-lead ECG is recommended every 12 to 18 months as a component of the screening algorithm for adolescent first-degree relatives of patients with HCM who have no evidence of hypertrophy on echocardiography. (*Level of Evidence: C*)
6. A 12-lead ECG is recommended as a component of the screening algorithm for first-degree relatives of patients with HCM. (*Level of Evidence: C*)

Class IIa

1. Twenty-four-hour ambulatory (Holter) electrocardiographic monitoring, repeated every 1 to 2 years, is reasonable in patients with HCM who have no previous evidence of VT to identify patients who may be candidates for ICD therapy.³³ (*Level of Evidence: C*)
2. Annual 12-lead ECGs are reasonable in patients with known HCM who are clinically stable to evaluate for asymptomatic changes in conduction or rhythm (ie, atrial fibrillation [AF]). (*Level of Evidence: C*)

Class IIb

1. Twenty-four-hour ambulatory (Holter) electrocardiographic monitoring might be considered in adults with HCM to assess for asymptomatic paroxysmal AF/atrial flutter. (*Level of Evidence: C*)

2.3. Echocardiography—Recommendations

Class I

1. A TTE is recommended in the initial evaluation of all patients with suspected HCM.^{34–41} (*Level of Evidence: B*)
2. A TTE is recommended as a component of the screening algorithm for family members of patients with HCM unless the family member is genotype negative in a family with known definitive mutations.^{42–45} (*Level of Evidence: B*)
3. Periodic (12 to 18 months) TTE screening is recommended for children of patients with HCM, starting by age 12 years or earlier if a growth spurt or signs of puberty are evident and/or when there are plans

for engaging in intense competitive sports or there is a family history of SCD.^{45,46} (*Level of Evidence: C*)

4. Repeat TTE is recommended for the evaluation of patients with HCM with a change in clinical status or new cardiovascular event.^{47–53} (*Level of Evidence: B*)
5. A transesophageal echocardiogram (TEE) is recommended for the intraoperative guidance of surgical myectomy.^{54–56} (*Level of Evidence: B*)
6. TTE or TEE with intracoronary contrast injection of the candidate's septal perforator(s) is recommended for the intraoperative guidance of alcohol septal ablation.^{57–60} (*Level of Evidence: B*)
7. TTE should be used to evaluate the effects of surgical myectomy or alcohol septal ablation for obstructive HCM.^{60–66} (*Level of Evidence: C*)

Class IIa

1. TTE studies performed every 1 to 2 years can be useful in the serial evaluation of symptomatically stable patients with HCM to assess the degree of myocardial hypertrophy, dynamic obstruction, and myocardial function.^{35,37,41} (*Level of Evidence: C*)
2. Exercise TTE can be useful in the detection and quantification of dynamic LVOT obstruction in the absence of resting outflow tract obstruction in patients with HCM.^{48,51,53,67,68} (*Level of Evidence: B*)
3. TEE can be useful if TTE is inconclusive for clinical decision making about medical therapy and in situations such as planning for myectomy, exclusion of subaortic membrane or mitral regurgitation secondary to structural abnormalities of the mitral valve apparatus, or in assessment for the feasibility of alcohol septal ablation.^{54–56} (*Level of Evidence: C*)
4. TTE combined with the injection of an intravenous contrast agent is reasonable if the diagnosis of apical HCM or apical infarction or severity of hypertrophy is in doubt, particularly when other imaging modalities such as cardiovascular magnetic resonance (CMR) are not readily available, not diagnostic, or are contraindicated. (*Level of Evidence: C*)
5. Serial TTE studies are reasonable for clinically unaffected patients who have a first-degree relative with HCM when genetic status is unknown. Such follow-up may be considered every 12 to 18 months for children or adolescents from high-risk families and every 5 years for adult family members.^{43–46} (*Level of Evidence: C*)

Class III: No Benefit

1. TTE studies should not be performed more frequently than every 12 months in patients with HCM when it is unlikely that any changes have occurred that would have an impact on clinical decision making. (*Level of Evidence: C*)
2. Routine TEE and/or contrast echocardiography is not recommended when TTE images are diagnostic of HCM and/or there is no suspicion of fixed ob-

struction or intrinsic mitral valve pathology. (*Level of Evidence: C*)

2.4. Stress Testing—Recommendations

Class IIa

1. Treadmill exercise testing is reasonable to determine functional capacity and response to therapy in patients with HCM. (*Level of Evidence: C*)
2. Treadmill testing with monitoring of an ECG and blood pressure is reasonable for SCD risk stratification in patients with HCM.^{69–71} (*Level of Evidence: B*)
3. In patients with HCM who do not have a resting peak instantaneous gradient of greater than or equal to 50 mm Hg, exercise echocardiography is reasonable for the detection and quantification of exercise-induced dynamic LVOT obstruction.^{67,70–72} (*Level of Evidence: B*)

2.5. Cardiac Magnetic Resonance—Recommendations

Class I

1. CMR imaging is indicated in patients with suspected HCM when echocardiography is inconclusive for diagnosis.^{73,74} (*Level of Evidence: B*)
2. CMR imaging is indicated in patients with known HCM when additional information that may have an impact on management or decision making regarding invasive management, such as magnitude and distribution of hypertrophy or anatomy of the mitral valve apparatus or papillary muscles, is not adequately defined with echocardiography.^{73–77} (*Level of Evidence: B*)

Class IIa

1. CMR imaging is reasonable in patients with HCM to define apical hypertrophy and/or aneurysm if echocardiography is inconclusive.^{73,75} (*Level of Evidence: B*)

Class IIb

1. In selected patients with known HCM, when SCD risk stratification is inconclusive after documentation of the conventional risk factors (Section 2.13), CMR imaging with assessment of late gadolinium enhancement (LGE) may be considered in resolving clinical decision making.^{78–82} (*Level of Evidence: C*)
2. CMR imaging may be considered in patients with LV hypertrophy and the suspicion of alternative diagnoses to HCM, including cardiac amyloidosis, Fabry disease, and genetic phenocopies such as *LAMP2* cardiomyopathy.^{83–85} (*Level of Evidence: C*)

2.6. Detection of Concomitant Coronary Disease—Recommendations

Class I

1. Coronary arteriography (invasive or computed tomographic imaging) is indicated in patients with HCM with chest discomfort who have an intermediate to high likelihood of coronary artery disease (CAD) when the identification of concomitant

CAD will change management strategies. (*Level of Evidence: C*)

Class IIa

1. Assessment of coronary anatomy with computed tomographic angiography (CTA) is reasonable for patients with HCM with chest discomfort and a low likelihood of CAD to assess for possible concomitant CAD. (*Level of Evidence: C*)
2. Assessment of ischemia or perfusion abnormalities suggestive of CAD with single photon emission computed tomography (SPECT) or positron emission tomography (PET) myocardial perfusion imaging (MPI; because of excellent negative predictive value) is reasonable in patients with HCM with chest discomfort and a low likelihood of CAD to rule out possible concomitant CAD. (*Level of Evidence: C*)

Class III: No Benefit

1. Routine SPECT MPI or stress echocardiography is not indicated for detection of “silent” CAD-related ischemia in patients with HCM who are asymptomatic. (*Level of Evidence: C*)
2. Assessment for the presence of blunted flow reserve (microvascular ischemia) using quantitative myocardial blood flow measurements by PET is not indicated for the assessment of prognosis in patients with HCM. (*Level of Evidence: C*)

2.7. Asymptomatic Patients—Recommendations

Class I

1. For patients with HCM, it is recommended that comorbidities that may contribute to cardiovascular disease (eg, hypertension, diabetes, hyperlipidemia, obesity) be treated in compliance with relevant existing guidelines.⁸⁶ (*Level of Evidence: C*)

Class IIa

1. Low-intensity aerobic exercise is reasonable as part of a healthy lifestyle for patients with HCM.^{32,87} (*Level of Evidence: C*)

Class IIb

1. The usefulness of beta blockade and calcium channel blockers to alter clinical outcome is not well established for the management of asymptomatic patients with HCM with or without obstruction.³² (*Level of Evidence: C*)

Class III: Harm

1. Septal reduction therapy should not be performed for asymptomatic adult and pediatric patients with HCM with normal effort tolerance regardless of the severity of obstruction.^{32,38} (*Level of Evidence: C*)
2. In patients with HCM with resting or provokable outflow tract obstruction, regardless of symptom

status, pure vasodilators and high-dose diuretics are potentially harmful.^{3,38} (*Level of Evidence: C*)

2.8. Pharmacologic Management—Recommendations

Class I

1. Beta-blocking drugs are recommended for the treatment of symptoms (angina or dyspnea) in adult patients with obstructive or nonobstructive HCM but should be used with caution in patients with sinus bradycardia or severe conduction disease.^{3,32,36,38,88–96} (*Level of Evidence: B*)
2. If low doses of beta-blocking drugs are ineffective for controlling symptoms (angina or dyspnea) in patients with HCM, it is useful to titrate the dose to a resting heart rate of less than 60 to 65 bpm (up to generally accepted and recommended maximum doses of these drugs).^{3,32,36,89–96} (*Level of Evidence: B*)
3. Verapamil therapy (starting in low doses and titrating up to 480 mg/d) is recommended for the treatment of symptoms (angina or dyspnea) in patients with obstructive or nonobstructive HCM who do not respond to beta-blocking drugs or who have side effects or contraindications to beta-blocking drugs. However, verapamil should be used with caution in patients with high gradients, advanced heart failure, or sinus bradycardia.^{32,36,88,97–101} (*Level of Evidence: B*)
4. Intravenous phenylephrine (or another pure vasoconstricting agent) is recommended for the treatment of acute hypotension in patients with obstructive HCM who do not respond to fluid administration.^{36,102–104} (*Level of Evidence: B*)

Class IIa

1. It is reasonable to combine disopyramide with a beta-blocking drug or verapamil in the treatment of symptoms (angina or dyspnea) in patients with obstructive HCM who do not respond to beta-blocking drugs or verapamil alone.^{32,36,88,105–108} (*Level of Evidence: B*)
2. It is reasonable to add oral diuretics in patients with nonobstructive HCM when dyspnea persists despite the use of beta blockers or verapamil or their combination.^{41,88} (*Level of Evidence: C*)

Class IIb

1. Beta-blocking drugs might be useful in the treatment of symptoms (angina or dyspnea) in children or adolescents with HCM, but patients treated with these drugs should be monitored for side effects, including depression, fatigue, or impaired scholastic performance. (*Level of Evidence: C*)
2. It may be reasonable to add oral diuretics with caution to patients with obstructive HCM when congestive symptoms persist despite the use of beta blockers or verapamil or their combination.^{32,36,88} (*Level of Evidence: C*)
3. The usefulness of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in the treatment of symptoms (angina or dyspnea) in patients with HCM with preserved systolic function is not well established, and these drugs should

be used cautiously (if at all) in patients with resting or provokable LVOT obstruction. (*Level of Evidence: C*)

4. In patients with HCM who do not tolerate verapamil or in whom verapamil is contraindicated, diltiazem may be considered. (*Level of Evidence: C*)

Class III: Harm

1. Nifedipine or other dihydropyridine calcium channel-blocking drugs are potentially harmful for treatment of symptoms (angina or dyspnea) in patients with HCM who have resting or provokable LVOT obstruction. (*Level of Evidence: C*)
2. Verapamil is potentially harmful in patients with obstructive HCM in the setting of systemic hypotension or severe dyspnea at rest. (*Level of Evidence: C*)
3. Digitalis is potentially harmful in the treatment of dyspnea in patients with HCM and in the absence of AF.^{3,32,36,109–111} (*Level of Evidence: B*)
4. The use of disopyramide alone without beta blockers or verapamil is potentially harmful in the treatment of symptoms (angina or dyspnea) in patients with HCM with AF because disopyramide may enhance atrioventricular conduction and increase the ventricular rate during episodes of AF.^{32,40,88,112–117} (*Level of Evidence: B*)
5. Dopamine, dobutamine, norepinephrine, and other intravenous positive inotropic drugs are potentially harmful for the treatment of acute hypotension in patients with obstructive HCM.^{3,102–104,118–121} (*Level of Evidence: B*)

2.9. Invasive Therapies—Recommendations

Class I

1. Septal reduction therapy should be performed only by experienced operators* in the context of a comprehensive HCM clinical program and only for the treatment of eligible patients with severe drug-refractory symptoms and LVOT obstruction.^{†122} (*Level of Evidence: C*)

*Experienced operators are defined as an individual operator with a cumulative case volume of at least 20 procedures or an individual operator who is working in a dedicated HCM program with a cumulative total of at least 50 procedures (Section 9.3.3).

†Eligible patients are defined by all of the following:

- a. Clinical: Severe dyspnea or chest pain (usually New York Heart Association [NYHA] functional classes III or IV) or occasionally other exertional symptoms (such as syncope or near syncope) that interfere with everyday activity or quality of life despite optimal medical therapy.
- b. Hemodynamic: Dynamic LVOT gradient at rest or with physiologic provocation ≥ 50 mm Hg associated with septal hypertrophy and systolic anterior motion (SAM) of the mitral valve.
- c. Anatomic: Targeted anterior septal thickness sufficient to perform the procedure safely and effectively in the judgment of the individual operator.

Class IIa

1. Consultation with centers experienced in performing both surgical septal myectomy and alcohol septal ablation is reasonable when discussing treatment options for eligible patients with HCM with severe drug-refractory symptoms and LVOT obstruction. (*Level of Evidence: C*)
2. Surgical septal myectomy, when performed in experienced centers, can be beneficial and is the first consideration for the majority of eligible patients with HCM with severe drug-refractory symptoms and LVOT obstruction.^{60,64,65,123–125} (*Level of Evidence: B*)
3. Surgical septal myectomy, when performed at experienced centers, can be beneficial in symptomatic children with HCM and severe resting obstruction (>50 mm Hg) for whom standard medical therapy has failed.¹²⁶ (*Level of Evidence: C*)
4. When surgery is contraindicated or the risk is considered unacceptable because of serious comorbidities or advanced age, alcohol septal ablation, when performed in experienced centers, can be beneficial in eligible adult patients with HCM with LVOT obstruction and severe drug-refractory symptoms (usually NYHA functional classes III or IV).^{60,62,127–131} (*Level of Evidence: B*)

Class IIb

1. Alcohol septal ablation, when performed in experienced centers, may be considered as an alternative to surgical myectomy for eligible adult patients with HCM with severe drug-refractory symptoms and LVOT obstruction when, after a balanced and thorough discussion, the patient expresses a preference for septal ablation.^{62,123,128,130,131} (*Level of Evidence: B*)
2. The effectiveness of alcohol septal ablation is uncertain in patients with HCM with marked (ie, >30 mm) septal hypertrophy, and therefore the procedure is generally discouraged in such patients. (*Level of Evidence: C*)

Class III: Harm

1. Septal reduction therapy should not be done for adult patients with HCM who are asymptomatic with normal exercise tolerance or whose symptoms are controlled or minimized on optimal medical therapy. (*Level of Evidence: C*)
2. Septal reduction therapy should not be done unless performed as part of a program dedicated to the longitudinal and multidisciplinary care of patients with HCM. (*Level of Evidence: C*)
3. Mitral valve replacement for relief of LVOT obstruction should not be performed in patients with HCM in whom septal reduction therapy is an option. (*Level of Evidence: C*)
4. Alcohol septal ablation should not be done in patients with HCM with concomitant disease that independently warrants surgical correction (eg, coronary artery bypass grafting for CAD, mitral valve repair for ruptured chordae) in whom surgical

myectomy can be performed as part of the operation. (*Level of Evidence: C*)

5. Alcohol septal ablation should not be done in patients with HCM who are less than 21 years of age and is discouraged in adults less than 40 years of age if myectomy is a viable option. (*Level of Evidence: C*)

See Data Supplement 2 for additional data regarding invasive therapies.

2.10. Pacing—Recommendations

Class IIa

1. In patients with HCM who have had a dual-chamber device implanted for non-HCM indications, it is reasonable to consider a trial of dual-chamber atrial-ventricular pacing (from the right ventricular apex) for the relief of symptoms attributable to LVOT obstruction.^{132–135} (*Level of Evidence: B*)

Class IIb

1. Permanent pacing may be considered in medically refractory symptomatic patients with obstructive HCM who are suboptimal candidates for septal reduction therapy.^{132–136} (*Level of Evidence: B*)

Class III: No Benefit

1. Permanent pacemaker implantation for the purpose of reducing gradient should not be performed in patients with HCM who are asymptomatic or whose symptoms are medically controlled.^{136–138} (*Level of Evidence: C*)
2. Permanent pacemaker implantation should not be performed as a first-line therapy to relieve symptoms in medically refractory symptomatic patients with HCM and LVOT obstruction who are candidates for septal reduction.^{136–138} (*Level of Evidence: B*)

See Data Supplement 3 for additional data regarding pacing.

2.11. Patients With LV Systolic Dysfunction—Recommendations

Class I

1. Patients with nonobstructive HCM who develop systolic dysfunction with an ejection fraction (EF) less than or equal to 50% should be treated according to evidence-based medical therapy for adults with other forms of heart failure with reduced EF, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, and other indicated drugs.^{49,139} (*Level of Evidence: B*)
2. Other concomitant causes of systolic dysfunction (such as CAD) should be considered as potential contributors to systolic dysfunction in patients with HCM. (*Level of Evidence: C*)

Class IIb

1. ICD therapy may be considered in adult patients with advanced (as defined by NYHA functional class III or IV heart failure) nonobstructive HCM, on maximal medical therapy, and EF less than or equal to 50%, who do not otherwise have an indication for an ICD.⁴⁹ (*Level of Evidence: C*)
2. For patients with HCM who develop systolic dysfunction, it may be reasonable to reassess the use of negative inotropic agents previously indicated, for example, verapamil, diltiazem, or disopyramide, and to consider discontinuing those therapies. (*Level of Evidence: C*)

2.12. Selection of Patients for Heart Transplantation—Recommendations

Class I

1. Patients with advanced heart failure (end-stage*) and nonobstructive HCM not otherwise amenable to other treatment interventions, with EF less than 50% (or occasionally with preserved EF), should be considered for heart transplantation.^{49,140} (*Level of Evidence: B*)
2. Symptomatic children with HCM with restrictive physiology who are not responsive to or appropriate candidates for other therapeutic interventions should be considered for heart transplantation.^{141,142} (*Level of Evidence: C*)

Class III: Harm

1. Heart transplantation should not be performed in mildly symptomatic patients of any age with HCM. (*Level of Evidence: C*)

2.13. SCD Risk Stratification—Recommendations

Class I

1. All patients with HCM should undergo comprehensive SCD risk stratification at initial evaluation to determine the presence of the following:^{30,31,143–152} (*Level of Evidence: B*)
 - a. A personal history for ventricular fibrillation, sustained VT, or SCD events, including appropriate ICD therapy for ventricular tachyarrhythmias.[†]
 - b. A family history for SCD events, including appropriate ICD therapy for ventricular tachyarrhythmias.[†]
 - c. Unexplained syncope.
 - d. Documented nonsustained ventricular tachycardia (NSVT) defined as 3 or more beats at greater than or equal to 120 bpm on ambulatory (Holter) ECG.
 - e. Maximal LV wall thickness greater than or equal to 30 mm.

*Characterized by systolic dysfunction (EF ≤50%), often associated with LV remodeling, including cavity enlargement and wall thinning, and because of diffuse myocardial scarring.

[†]Appropriate ICD discharge is defined as ICD therapy triggered by VT or ventricular fibrillation, documented by stored intracardiac electrogram or cycle-length data, in conjunction with the patient's symptoms immediately before and after device discharge.

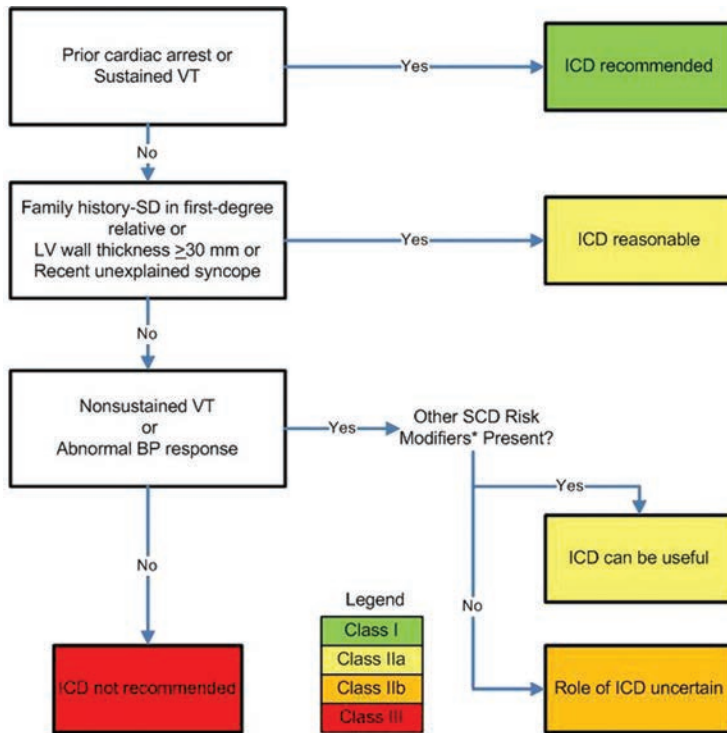


Figure 1. Indications for ICDs in HCM. *SCD risk modifiers include established risk factors and emerging risk modifiers (Section 9.4.2). BP indicates blood pressure; ICD, implantable cardioverter-defibrillator; LV, left ventricular; SCD, sudden cardiac death; SD, sudden death; and VT, ventricular tachycardia.

Regardless of the level of recommendation put forth in these guidelines, the decision for placement of an ICD must involve prudent application of individual clinical judgment, thorough discussions of the strength of evidence, the benefits, and the risks (including but not limited to inappropriate discharges, lead and procedural complications) to allow active participation of the fully informed patient in ultimate decision making.

Class IIa

1. It is reasonable to assess blood pressure response during exercise as part of SCD risk stratification in patients with HCM.^{30,71,149} (Level of Evidence: B)
2. SCD risk stratification is reasonable on a periodic basis (every 12 to 24 months) for patients with HCM who have not undergone ICD implantation but would otherwise be eligible in the event that risk factors are identified (12 to 24 months). (Level of Evidence: C)

Class IIb

1. The usefulness of the following potential SCD risk modifiers is unclear but might be considered in selected patients with HCM for whom risk remains borderline after documentation of conventional risk factors:
 - a. CMR imaging with LGE.^{78,82} (Level of Evidence: C)
 - b. Double and compound mutations (ie, >1). (Level of Evidence: C)
 - c. Marked LVOT obstruction.^{30,48,51,149} (Level of Evidence: B)

Class III: Harm

1. Invasive electrophysiologic testing as routine SCD risk stratification for patients with HCM should not be performed. (Level of Evidence: C)

See Data Supplement 4 for additional data regarding SCD risk stratification.

2.14. Selection of Patients for ICDs—Recommendations

Class I

1. The decision to place an ICD in patients with HCM should include application of individual clinical judgment, as well as a thorough discussion of the strength of evidence, benefits, and risks to allow the informed patient's active participation in decision making (Figure 1).^{144,150,153,154} (Level of Evidence: C)
2. ICD placement is recommended for patients with HCM with prior documented cardiac arrest, ventricular fibrillation, or hemodynamically significant VT.^{145,146,148,150} (Level of Evidence: B)

Class IIa

1. It is reasonable to recommend an ICD for patients with HCM with:
 - a. Sudden death presumably caused by HCM in 1 or more first-degree relatives.¹⁵⁵ (Level of Evidence: C)
 - b. A maximum LV wall thickness greater than or equal to 30 mm.^{147,156–158} (Level of Evidence: C)
 - c. One or more recent, unexplained syncopal episodes.¹⁵² (Level of Evidence: C)

2. An ICD can be useful in select patients with NSVT (particularly those <30 years of age) in the presence of other SCD risk factors or modifiers.^{‡33,144} (*Level of Evidence: C*)
3. An ICD can be useful in select patients with HCM with an abnormal blood pressure response with exercise in the presence of other SCD risk factors or modifiers.^{‡70,71,149} (*Level of Evidence: C*)
4. It is reasonable to recommend an ICD for high-risk children with HCM, based on unexplained syncope, massive LV hypertrophy, or family history of SCD, after taking into account the relatively high complication rate of long-term ICD implantation. (*Level of Evidence: C*)

Class IIb

1. The usefulness of an ICD is uncertain in patients with HCM with isolated bursts of NSVT when in the absence of any other SCD risk factors or modifiers.^{‡144} (*Level of Evidence: C*)
2. The usefulness of an ICD is uncertain in patients with HCM with an abnormal blood pressure response with exercise when in the absence of any other SCD risk factors or modifiers,[‡] particularly in the presence of significant outflow obstruction.^{70,71,149} (*Level of Evidence: C*)

Class III: Harm

1. ICD placement as a routine strategy in patients with HCM without an indication of increased risk is potentially harmful. (*Level of Evidence: C*)
2. ICD placement as a strategy to permit patients with HCM to participate in competitive athletics is potentially harmful. (*Level of Evidence: C*)
3. ICD placement in patients who have an identified HCM genotype in the absence of clinical manifestations of HCM is potentially harmful. (*Level of Evidence: C*)

2.15. Selection of ICD Device Type—Recommendations

Class IIa

1. In patients with HCM who meet indications for ICD implantation, single-chamber devices are reasonable in younger patients without a need for atrial or ventricular pacing.^{159–162} (*Level of Evidence: B*)
2. In patients with HCM who meet indications for ICD implantation, dual-chamber ICDs are reasonable for patients with sinus bradycardia and/or paroxysmal AF.¹⁵⁹ (*Level of Evidence: C*)
3. In patients with HCM who meet indications for ICD implantation, dual-chamber ICDs are reasonable for patients with elevated resting outflow gradients greater than 50 mm Hg and significant heart failure symptoms who may benefit from right ventricular pacing (most commonly, but not limited to, patients >65 years of age).^{136–138,159} (*Level of Evidence: B*)

2.16. Participation in Competitive or Recreational Sports and Physical Activity—Recommendations

Class IIa

1. It is reasonable for patients with HCM to participate in low-intensity competitive sports (eg, golf and bowling).^{163,164} (*Level of Evidence: C*)
2. It is reasonable for patients with HCM to participate in a range of recreational sporting activities as outlined in Table 2.⁸⁷ (*Level of Evidence: C*)

Class III: Harm

1. Patients with HCM should not participate in intense competitive sports regardless of age, sex, race, presence or absence of LVOT obstruction, prior septal reduction therapy, or implantation of a cardioverter-defibrillator for high-risk status.^{163–169} (*Level of Evidence: C*)

2.17. Management of AF—Recommendations

Class I

1. Anticoagulation with vitamin K antagonists (ie, warfarin, to an international normalized ratio of 2.0 to 3.0) is indicated in patients with paroxysmal, persistent, or chronic AF and HCM.^{170–172} (Anticoagulation with direct thrombin inhibitors [ie, dabigatran[§]] may represent another option to reduce the risk of thromboembolic events, but data for patients with HCM are not available.¹⁷³) (*Level of Evidence: C*)
2. Ventricular rate control in patients with HCM with AF is indicated for rapid ventricular rates and can require high doses of beta antagonists and nondihydropyridine calcium channel blockers.^{170,172} (*Level of Evidence: C*)

Class IIa

1. Disopyramide (with ventricular rate-controlling agents) and amiodarone are reasonable antiarrhythmic agents for AF in patients with HCM.^{170,174} (*Level of Evidence: B*)
2. Radiofrequency ablation for AF can be beneficial in patients with HCM who have refractory symptoms or who are unable to take antiarrhythmic drugs.^{175–179} (*Level of Evidence: B*)
3. Maze procedure with closure of left atrial appendage is reasonable in patients with HCM with a history of AF, either during septal myectomy or as an isolated procedure in selected patients. (*Level of Evidence: C*)

Class IIb

1. Sotalol, dofetilide, and dronedarone might be considered alternative antiarrhythmic agents in patients with HCM, especially in those with an ICD, but clinical experience is limited. (*Level of Evidence: C*)

[‡]SCD risk modifiers are discussed in Section 9.4.2.

[§]Dabigatran should not be used in patients with prosthetic valves, hemodynamically significant valve disease, advanced liver failure, or severe renal failure (creatinine clearance <15 mL/min).¹⁷³

Table 2. Recommendations for the Acceptability of Recreational (Noncompetitive) Sports Activities and Exercise in Patients With HCM*

Intensity Level	Eligibility Scale for HCM†
High	
Basketball (full court)	0
Basketball (half court)	0
Body building‡	1
Gymnastics	2
Ice hockey‡	0
Racquetball/squash	0
Rock climbing‡	1
Running (sprinting)	0
Skiing (downhill)‡	2
Skiing (cross-country)	2
Soccer	0
Tennis (singles)	0
Touch (flag) football	1
Windsurfing§	1
Moderate	
Baseball/softball	2
Biking	4
Hiking	3
Modest hiking	4
Motorcycling‡	3
Jogging	3
Sailing§	3
Surfing§	2
Swimming (laps)§	5
Tennis (doubles)	4
Treadmill/stationary bicycle	5
Weightlifting (free weights)‡	1
Low	
Bowling	5
Brisk walking	5
Golf	5
Horseback riding‡	3
Scuba diving§	0
Skating¶	5
Snorkeling§	5
Weights (nonfree weights)	4

*Recreational sports are categorized according to high, moderate, and low levels of exercise and graded on a relative scale (from 0 to 5) for eligibility, with 0 to 1 indicating generally not advised or strongly discouraged; 4 to 5, probably permitted; and 2 to 3, intermediate and to be assessed clinically on an individual basis. The designations of high, moderate, and low levels of exercise are equivalent to an estimated >6, 4 to 6, and <4 metabolic equivalents, respectively.

†Assumes absence of laboratory DNA genotyping data; therefore, limited to clinical diagnosis.

‡These sports involve the potential for traumatic injury, which should be taken into consideration for individuals with a risk for impaired consciousness.

§The possibility of impaired consciousness occurring during water-related activities should be taken into account with respect to the individual patient's clinical profile.

||Recommendations generally differ from those for weight-training machines (nonfree weights), based largely on the potential risks of traumatic injury associated with episodes of impaired consciousness during bench-press maneuvers; otherwise, the physiologic effects of all weight-training activities are regarded as similar with respect to the present recommendations.

¶Individual sporting activity not associated with the team sport of ice hockey.

Adapted with permission from Maron et al.⁸⁷

2.18. Pregnancy/Delivery—Recommendations

Class I

1. In women with HCM who are asymptomatic or whose symptoms are controlled with beta-blocking drugs, the drugs should be continued during pregnancy, but increased surveillance for fetal bradycardia or other complications is warranted.^{43,44,180,181} (*Level of Evidence: C*)
2. For patients (mother or father) with HCM, genetic counseling is indicated before planned conception. (*Level of Evidence: C*)
3. In women with HCM and resting or provokable LVOT obstruction greater than or equal to 50 mm Hg and/or cardiac symptoms not controlled by medical therapy alone, pregnancy is associated with increased risk, and these patients should be referred to a high-risk obstetrician. (*Level of Evidence: C*)
4. The diagnosis of HCM among asymptomatic women is not considered a contraindication for pregnancy, but patients should be carefully evaluated in regard to the risk of pregnancy. (*Level of Evidence: C*)

Class IIa

1. For women with HCM whose symptoms are controlled (mild to moderate), pregnancy is reasonable, but expert maternal/fetal medical specialist care, including cardiovascular and prenatal monitoring, is advised. (*Level of Evidence: C*)

Class III: Harm

1. For women with advanced heart failure symptoms and HCM, pregnancy is associated with excess morbidity/mortality. (*Level of Evidence: C*)

3. Prevalence/Nomenclature/Differential Diagnosis

3.1. Prevalence

HCM is a common genetic cardiovascular disease. In addition, HCM is a global disease,¹⁸² with epidemiological studies from several parts of the world¹⁸³ reporting a similar prevalence of LV hypertrophy, the quintessential phenotype of HCM, to be about 0.2% (ie, 1:500) in the general population, which is equivalent to at least 600 000 people affected in the United States.¹⁸⁴

3.1.1. Clinical Definition and Differential Diagnosis

HCM is the preferred nomenclature to describe this disease,¹⁸⁵ although confusion over the names used to characterize this entity has arisen over the years in part because one third of patients have no obstruction either at rest or with physiologic provocation.⁶⁷ The generally accepted definition of HCM is a disease state characterized by unexplained LV hypertrophy associated with nondilated ventricular chambers in the absence of another cardiac or systemic disease that itself would be capable of producing the magnitude of hypertrophy evident in a given patient,^{32,38,184–187} with the caveat that patients who are genotype positive may be phenotypically negative without overt hypertrophy.^{188,189} Clinically, HCM is

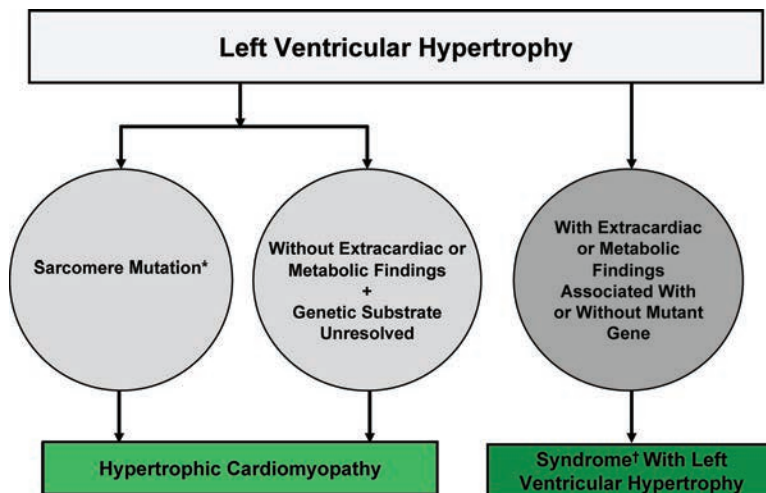


Figure 2. Summary of the nomenclature that distinguishes HCM from other genetic diseases associated with LV hypertrophy. *At this time the overwhelming evidence links the clinical diagnosis of HCM with a variety of genes encoding protein components of the cardiac sarcomere. However, it is possible that in the future other non-sarcomeric (but also nonmetabolic) genes may prove to cause HCM. †An example is Noonan syndrome with cardiomyopathy. Modified with permission from Maron et al.¹⁸⁷

usually recognized by a maximal LV wall thickness ≥ 15 mm. In the case of children, increased LV wall thickness is defined as wall thickness ≥ 2 standard deviations above the mean (z score ≥ 2) for age, sex, or body size. However, it should be underscored that in principle, any degree of wall thickness is compatible with the presence of the HCM genetic substrate. Furthermore, although a myriad of patterns and distribution of LV hypertrophy (including diffuse and marked) have been reported in HCM,^{37,76,190} about one third of patients have largely segmental wall thickening involving only a small portion of the left ventricle, and indeed, such patients with HCM usually have normal calculated LV mass.⁷⁶

Differential diagnosis of HCM and other cardiac conditions (with LV hypertrophy) may arise, most commonly with hypertensive heart disease and the physiologic remodeling associated with athletic training (“athlete’s heart”),^{191–195} usually when maximum wall thickness is in the modest range of 13 to 15 mm.

These important distinctions are often resolved by noninvasive markers, including sarcomeric mutations or family history of HCM, LV cavity dimension, diastolic function, pattern of LV hypertrophy, or short deconditioning periods.^{191–195}

It is evident that metabolic or infiltrative storage disorders with LV hypertrophy in babies, older children, and young adults can mimic clinically diagnosed HCM (attributable to sarcomeric protein mutations), for example, conditions such as mitochondrial disease,^{196,197} Fabry disease,¹⁹⁸ or storage diseases caused by mutations in the genes encoding the γ -2-regulatory subunit of the adenosine monophosphate (AMP)-activated protein kinase (PRKAG2) or the X-linked lysosome-associated membrane protein gene (*LAMP2*; Danon disease).^{4,199–201} Use of the term HCM is not appropriate to describe these and other patients with LV hypertrophy that occurs in the context of a multisystem disorder^{202–206} (Figure 2). In addition, differential diagnosis of HCM may require distinction from dilated cardiomyopathy when HCM presents in the end stage.⁴⁹

3.1.2. Impact of Genetics

On the basis of the genotype-phenotype data available at this time, HCM is regarded here as a disease entity caused by

autosomal dominant mutations in genes encoding protein components of the sarcomere and its constituent myofilament elements.^{43,199,207,208} Intergenetic diversity is compounded by considerable intragene heterogeneity, with >1400 mutations identified among at least 8 genes. The current weight of evidence supports the view that the vast majority of genes and mutations responsible for clinically diagnosed HCM encode proteins within and associated with the sarcomere, accounting in large measure for those patients described in the voluminous amount of HCM literature published over 50 years.^{43,199,207,208}

3.1.3. HCM Centers

The writing committee considers it important to emphasize that HCM is a complex disease entity with a broad (and increasing) clinical and genetic spectrum.³⁸ Although HCM is one of the most common forms of genetic heart disease and relatively common in the general population,¹⁸⁴ this disease entity is infrequent in general clinical practice, with most cardiologists responsible for the care of only a few patients with HCM.²⁰⁹ This principle has led to an impetus for establishing clinical programs of excellence—usually within established centers—in which cardiovascular care is focused on the management of HCM (ie, “HCM centers”).^{209,210}

4. Clinical Course and Natural History, Including Absence of Complications

HCM is a heterogeneous cardiac disease with a diverse clinical presentation and course, presenting in all age groups from infancy to the very elderly.^{32,38,49,51} Most affected individuals probably achieve a normal life expectancy without disability or the necessity for major therapeutic interventions.^{211–214} On the other hand, in some patients, HCM is associated with disease complications that may be profound, with the potential to result in disease progression or premature death.^{32,38,49,51,147,156} When the disease does result in significant complications, there are 3 relatively discrete but not mutually exclusive pathways of clinical progression (Figure 3):

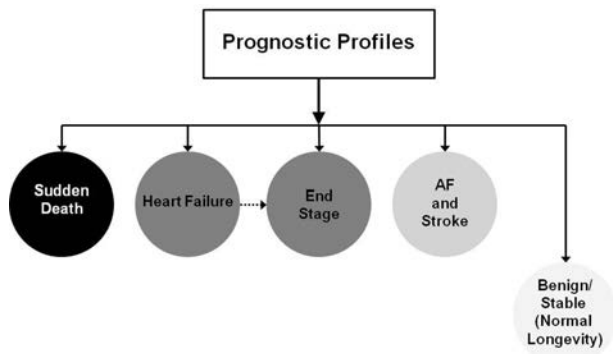


Figure 3. Prognosis profiles for HCM and targets for therapy. AF indicates atrial fibrillation. Modified with permission from Maron et al.³²

1. SCD due to unpredictable ventricular tachyarrhythmias, most commonly in asymptomatic patients <35 years of age^{50,144,147,150,153,154,156,166,168,215} (including competitive athletes).^{166,168}
2. Heart failure characterized by exertional dyspnea (with or without chest pain) that may be progressive.⁴⁹
3. AF, also associated with various degrees of heart failure¹⁷² and an increased risk of systemic thromboembolism and stroke.

The natural history of HCM can be altered by a number of therapeutic interventions: ICDs for secondary or primary prevention of sudden death in patients with risk factors^{150,153,154}; drugs appropriate to control heart failure symptoms (principally those of exertional dyspnea and chest discomfort),^{32,38} surgical septal myectomy⁶⁴ or alcohol septal ablation⁶⁰ for progressive and drug-refractory heart failure caused by LVOT obstruction; heart transplantation for systolic (or less frequently, intractable diastolic) dysfunction associated with severe unrelenting symptoms⁴⁹; and drug therapy or possibly radiofrequency ablation or surgical maze procedure for AF.^{175,178,179}

5. Pathophysiology

The pathophysiology of HCM is complex and consists of multiple interrelated abnormalities, including LVOT obstruction, diastolic dysfunction, mitral regurgitation, myocardial ischemia, and arrhythmias.^{38,40,41} It is clinically important to distinguish between the obstructive and nonobstructive forms of HCM because management strategies are largely dependent on the presence or absence of symptoms caused by obstruction.

5.1. LVOT Obstruction

The original observations by Brock²¹⁶ and Braunwald et al³ emphasized the functional subvalvular LVOT gradient, which was highly influenced by alterations in the load and contractility of the left ventricle. The clinical significance of the outflow tract gradient has periodically been controversial,^{217–220} but careful studies have shown definitively that true mechanical obstruction to outflow does occur.^{40,41} For HCM, it is the peak instantaneous LV outflow gradient rather than the mean gradient that influences treatment decisions (Table 3).

Outflow obstruction usually occurs in HCM by virtue of mitral valve SAM and mitral-septal contact. Muscular ob-

Table 3. Definitions of Dynamic Left Ventricular Outflow Tract Obstruction

Hemodynamic State	Conditions	Outflow Gradient*
Basal obstruction	Rest	≥30 mm Hg†
Nonobstructive	Rest	<30 mm Hg
	Physiologically provoked	<30 mm Hg
Labile obstruction	Rest	<30 mm Hg†
	Physiologically provoked	≥30 mm Hg†

*Either the peak instantaneous continuous wave Doppler gradient or the peak-to-peak cardiac catheterization gradient, which are equivalent in hypertrophic cardiomyopathy.^{221,222}

†Gradients ≥50 mm Hg either at rest or with provocation are considered the threshold for septal reduction therapy in severely symptomatic patients.

struction can also be present in the midcavitary region, occasionally because of hypertrophied papillary muscles abutting the septum²²³ or anomalous papillary muscle insertion into the anterior mitral leaflet.²²⁴

Obstruction to LV outflow is dynamic, varying with loading conditions and contractility of the ventricle.³ Increased myocardial contractility, decreased ventricular volume, or decreased afterload increases the degree of subaortic obstruction. Patients may have little or no obstruction of the LVOT at rest but can generate large LVOT gradients under conditions such as exercise, the strain phase of the Valsalva maneuver, or during pharmacologic provocation.^{40,41} There is often large spontaneous variation in the severity of the gradient during day-to-day activities or even with food or alcohol intake²²⁵; exacerbation of symptoms during the postprandial period is common. Importantly, it has been well established that LVOT obstruction contributes to the debilitating heart failure-related symptoms that may occur in HCM,^{40,41} and is also a major determinant of outcome.⁵¹

The presence and magnitude of outflow obstruction are usually assessed with 2-dimensional echocardiography and continuous wave Doppler. Combining exercise testing with Doppler echocardiography is useful in identifying the presence of physiologically provokable LVOT obstruction and is particularly helpful in patients with symptoms during routine physical activities who do not manifest outflow obstruction at rest.⁶⁷ Provocation with dobutamine infusion during Doppler echocardiography is no longer recommended as a strategy to induce outflow gradients in HCM.

6. Diagnosis

The clinical diagnosis of HCM is conventionally made with cardiac imaging, at present most commonly with 2-dimensional echocardiography and increasingly with CMR. Morphologic diagnosis is based on the presence of a hypertrophied and nondilated left ventricle in the absence of another cardiac or systemic disease capable of producing the magnitude of hypertrophy evident in a patient (usually ≥15 mm in an adult or the equivalent relative to body surface area in children). Genetic testing, which is now commercially available, is a powerful strategy for definitive diagnosis of affected genetic status and is currently used most effectively

in the identification of affected relatives in families known to have HCM.

HCM is caused by an autosomal dominant mutation in genes that encode sarcomere proteins or sarcomere-associated proteins. The most vigorous evidence indicates that 8 genes are known to definitively cause HCM: beta myosin heavy chain, myosin binding protein C, troponin T, troponin I, alpha tropomyosin, actin, regulatory light chain, and essential light chain.^{43,186,187,199,207,208} In addition, actinin and myozenin are associated with less definitive evidence for causing HCM. At this time there is inconclusive evidence to support other genes causing HCM,^{7,9,226,227} but research is ongoing.^{6,228} A single mutation in 1 of the 2 alleles (or copies) of a gene is sufficient to cause HCM; however, 5% of patients with HCM have ≥ 2 mutations in the same or different genes.^{23,229}

Genetic and/or clinical screening of all first-degree family members of patients with HCM is important to identify those with unrecognized disease. On the basis of family history, clinical screening, and pedigree analyses, the pattern of inheritance is ascertained to identify and counsel relatives at risk.¹⁴ Because familial HCM is a dominant disorder, the risk that an affected patient will transmit disease to each offspring is 50%. When a pathogenic mutation is identified in an index patient, the genetic status of each family member can be readily ascertained.

Because unrelated patients with HCM will have different mutations, a comprehensive sequence-based analysis of all HCM genes is necessary to define the pathogenic (eg, disease causing) mutation in an index patient. Experienced clinical laboratories identify the pathogenic HCM mutation in approximately 60% to 70% of patients with a positive family history and approximately 10% to 50% of patients without a family history.^{6,15} Genetic testing may identify a pathogenic mutation (eg, analysis defines a sequence variant known to cause HCM) or a “likely pathogenic” mutation, a DNA variant that was previously *unknown* as a cause of HCM but has molecular characteristics that are similar to recognized HCM mutations. Genetic testing may also identify “variants of uncertain significance.” Studies suggest that the presence of >1 HCM-associated sarcomere mutation is associated with greater severity of disease.^{23,24,230,231}

When genetic testing reveals a mutation in the index patient, ascertainment of genetic status in first-degree relatives can be predictive of risk for developing HCM.¹⁸ Genetic counseling should precede genetic testing of family members.¹⁴ Relatives with overt HCM will have the same pathogenic HCM mutation as the index patient. Pathogenic mutations may also be identified in other relatives with unknown clinical status. These mutation carriers should be evaluated by physical examination, electrocardiography, and 2-dimensional echocardiography, and if HCM is identified, these individuals should undergo risk stratification (Section 2.13). Mutation carriers without evidence of HCM (genotype positive/phenotype negative) are at considerable risk for future development of HCM, and guidelines to evaluate these individuals are discussed below.^{188,189} Mutation-negative family members and their descendants have no risk for developing HCM and do not need further

Table 4. Proposed Clinical Screening Strategies With Echocardiography (and 12-Lead ECG) for Detection of Hypertrophic Cardiomyopathy With Left Ventricular Hypertrophy in Families*

Age <12 y	
Optional unless	
	Malignant family history of premature death from HCM or other adverse complications
	Patient is a competitive athlete in an intense training program
	Onset of symptoms
	Other clinical suspicion of early LV hypertrophy
Age 12 to 18–21 y†	
Every 12–18 mo	
Age >18 –21 y	
At onset of symptoms or at least every 5 y. More frequent intervals are appropriate in families with a malignant clinical course or late-onset HCM	

*When pathologic mutations are not identified or genetic testing is either ambiguous or not performed.

†Age range takes into consideration individual variability in achieving physical maturity and in some patients may justify screening at an earlier age. Initial evaluation should occur no later than early pubescence.²³³

ECG indicates electrocardiogram; HCM, hypertrophic cardiomyopathy; and LV, left ventricular.

evaluation. Information from genotyping may help define clinical manifestations and outcomes in specific families with HCM (Table 4).^{7–9,18,20–22,232}

6.1. Cardiovascular Magnetic Resonance

CMR provides superior spatial resolution with sharp contrast between blood and myocardium, as well as tomographic imaging of the entire LV myocardium and therefore the opportunity to more accurately characterize the presence and distribution of LV hypertrophy in HCM.

Two-dimensional echocardiography has demonstrated the heterogeneity of the hypertrophic phenotype in patients with HCM, particularly with regard to distribution of LV hypertrophy and mechanisms of outflow obstruction.^{32,38,67,76,190,220,234} However, there remain patients in whom the diagnosis of HCM is suspected but the echocardiogram is inconclusive, mostly because of suboptimal imaging from poor acoustic windows or when hypertrophy is localized to regions of the LV myocardium not well visualized by echocardiography.⁷⁶ In 1 study, 6% of patients with suspected HCM were identified with increased LV wall thickness (predominantly in the anterolateral wall) by CMR but not by echocardiography.^{74,76,77} In addition, hypertrophy confined to the apex (ie, apical HCM) may be difficult to visualize with echocardiography but is evident with CMR.^{73,75} Furthermore, CMR can more readily detect the presence of apical aneurysms (particularly when small). The latter has potential implications for management with ICDs and/or anticoagulation. The magnitude of LV wall thickening may be underestimated by echocardiography compared with CMR, particularly when this region involves the anterolateral free wall,^{76,77} and therefore CMR may identify high-risk status on the basis of massive hypertrophy. Accurate characterization of the HCM phenotype by CMR may also be useful

in management decisions for invasive therapies (septal myectomy or alcohol septal ablation) by more precisely defining the location and magnitude of hypertrophy, as well as characterizing the mitral and submitral apparatus and papillary muscles.^{235,236}

The opportunity for contrast-enhanced CMR with LGE to identify areas of myocardial fibrosis in patients with HCM has been the subject of a growing literature.^{79–81,237,238} Although patients with the end-stage phenotype almost universally demonstrate such findings,⁴⁹ patients with HCM with preserved systolic function may also have areas of LGE.^{79–81} Importantly, patients with HCM with evidence of LGE on CMR imaging tend to have more markers of risk of SCD, such as NSVT on Holter monitoring, than patients without LGE.^{78,80}

It is plausible that areas of LGE (ie, probably largely replacement myocardial fibrosis) could represent a substrate for the generation of malignant ventricular tachyarrhythmias in HCM. Several studies have addressed this issue and have reported either trends in such a direction or significant associations between the presence of LGE (not extent) and cardiac outcome events.^{81,239} However, there is insufficient evidence at this time to support a significant association between the extent of LGE and outcome. Nonetheless, the present data would support a potential role of LGE as an arbitrator in decision making for primary prevention ICDs in patients in whom risk status remains uncertain after assessment of conventional risk markers.^{79,80}

7. Concomitant Coronary Disease

Chest discomfort is a common symptom in patients with HCM. A key management issue revolves around whether the discomfort may be caused by concomitant epicardial obstructive CAD with inducible ischemia or a consequence of microvascular dysfunction.³⁸ Concomitant presence of CAD in patients with HCM identifies a higher risk for adverse outcomes and potential candidates for revascularization.^{240,241}

Myocardial bridging of the left anterior descending coronary artery is a frequent component of phenotypically expressed HCM and more common than in other diseases with or without LV hypertrophy. Although it has been suggested that ischemia secondary to bridging could be a potential mechanism for sudden death in HCM,²⁴² there is no consistent evidence to support this hypothesis in either adults or children.^{243,244}

8. Choice of Imaging Modality

8.1. Invasive Coronary Arteriography

Invasive coronary arteriography is indicated in patients with HCM when knowledge of these features will importantly influence management strategies. Coronary arteriography should be undertaken before alcohol septal ablation in order to define the anatomy of the septal perforators and exclude obstructive coronary stenoses.

8.2. Noninvasive CTA

Although there are no published data specifically assessing the performance characteristics of CTA for documenting the presence or absence of epicardial CAD in HCM, there is no

reason to believe that performance of the test should differ in patients with HCM. A high negative predictive value to exclude CAD is particularly consistent in the literature.

8.3. Single Photon Emission Computed Tomography Myocardial Perfusion Imaging

Stress SPECT MPI in patients with HCM will often demonstrate reversible or fixed perfusion defects consistent with ischemia or infarction, respectively, even in the absence of epicardial CAD.^{245,246} Several lines of evidence support that these defects, even in the absence of symptoms, represent true flow abnormalities and possibly “silent” ischemia.²⁴⁷

Fixed defects may also be seen with SPECT MPI, a finding consistent with infarction. These patients will often have the “end-stage” clinical phenotype with reduced EF²⁴⁵ and likely correspond to patients who demonstrate LGE in CMR studies.⁴⁹

8.4. Positron Emission Tomography

PET imaging has been used in patients with HCM to study myocardial blood flow, as well as myocardial metabolism. In patients with HCM with normal coronary arteries, myocardial perfusion PET studies have shown that although resting myocardial blood flow may be similar to normal control subjects, the augmentation of blood flow with vasodilation, for example, dipyridamole, may be significantly blunted.^{248–251} However, the quantitative PET techniques used in these studies are not part of routine clinical practice, and the management implications of identifying abnormalities in flow reserve are unresolved.

8.5. Stress Echocardiography

There are no published studies addressing the performance characteristics of stress echocardiography to detect or exclude CAD in patients with HCM. Patients with HCM have heterogeneous wall-thickness patterns, and wall motion at rest may appear abnormal in regions of hypertrophied myocardium. Therefore, stress echocardiography to detect or rule out CAD may be unreliable in HCM but may be useful to document the presence or magnitude of outflow tract obstruction generated by exercise⁶⁷ (Section 5.1).

9. Management of HCM

Treatment of patients with HCM requires a thorough understanding of the complex, diverse pathophysiology and natural history and must be individualized to the patient, but the general approach of the writing committee is outlined in Figure 4.

9.1. Asymptomatic Patients

A large proportion of patients presenting with HCM are asymptomatic, and most will achieve a normal life expectancy.^{213,252,253} It is essential to educate these patients and their families about the disease process, including screening of first-degree relatives and avoiding particularly strenuous activity or competitive athletics.⁸⁸ Risk stratification for SCD should also be performed in all patients, irrespective of whether symptoms are present.^{32,38}

prolongs the diastolic filling period, which may allow for more efficient inactivation of myocardial contractile proteins, thereby improving diastolic filling.^{255,256}

In those patients unable to tolerate beta blockers or those with symptoms unresponsive to beta blockers, calcium channel blockers may provide effective symptomatic relief. Verapamil has been the most intensively studied such agent (Figure 4).^{99,257} Possible mechanisms for symptomatic improvement include negative inotropic and rate-lowering effects similar to those of beta blockers. However, the effect of verapamil on diastolic dysfunction is controversial.^{258–262} Diltiazem has also been shown to improve measures of diastolic performance²⁶³ and to prevent or diminish myocardial ischemia.²⁶⁴ Both verapamil and diltiazem should be used cautiously in patients with severe outflow tract obstruction, elevated pulmonary artery wedge pressure, and low systemic blood pressure, because a decrease in blood pressure with treatment may trigger an increase in outflow obstruction and precipitate pulmonary edema. Administration of beta-blocking drugs with either verapamil or diltiazem should also be used with caution because of the potential for high-grade atrioventricular block. Dihydropyridine class calcium channel blockers (eg, nifedipine) should not be used in patients with obstructive physiology because their vasodilatory effects may aggravate outflow obstruction.

In patients with obstructive HCM who remain symptomatic despite the use of beta blockers and calcium channel blockers, alone or in combination, disopyramide may be effective in ameliorating symptoms (Figure 4).^{68,265} Diuretics may be effective for symptomatic relief in patients with pulmonary congestion but should be used judiciously in those with outflow tract obstruction at rest or with provocation.

9.3. Invasive Therapies

For severe refractory symptoms that are attributable to LVOT obstruction, invasive therapies can be used to improve quality of life (Figure 4). Surgical approaches have been used for 5 decades^{52,220} so that relief of outflow tract obstruction and symptoms can be achieved with minimal perioperative morbidity or mortality in experienced centers.^{64,65} However, some patients are not optimal surgical candidates (eg, because of comorbidities or advanced age) or have such a strong desire to avoid surgery that alternative therapeutic interventions have been implemented. Alcohol septal ablation, which has been used for the past 17 years, has become the leading strategy in these circumstances.²⁶⁶

9.3.1. Selection of Patients

It is well recognized that the appropriate selection of patients for individual procedures is an important predictor of outcome. Because the majority of patients with HCM can achieve control of their symptoms with optimal pharmacologic therapy, and in light of the complications inherent with invasive therapies, a core set of clinical, anatomic, and hemodynamic criteria are required before patients are considered candidates for invasive therapies. Specifically, patients must have symptoms attributable to LVOT obstruction that are refractory to optimal pharmacologic therapy. Similarly, it must be demonstrated that the obstruction is caused

by apposition of the mitral valve with the hypertrophied septum.^{52,220} Maximal instantaneous gradients of at least 50 mm Hg at rest or with physiologic provocation are necessary to produce symptoms amenable to invasive therapies.³²

Given the duration of experience, documented long-term results, and safety data, surgical septal myectomy is considered the preferred treatment for most patients who meet these criteria (Figure 4). Considerations that favor surgical intervention include younger age, greater septal thickness, and concomitant cardiac disease independently requiring surgical correction (eg, intrinsic mitral valve disease or coronary artery bypass grafting). Additionally, specific abnormalities of the mitral valve and its support apparatus can contribute significantly to the generation of outflow tract obstruction, suggesting the potential value of additional surgical approaches (eg, plication, valvuloplasty, and papillary muscle relocation) and making myectomy more appropriate than alcohol septal ablation in some patients.^{26,224,267–272} Among patients who meet the core selection criteria, factors that influence a decision to proceed with alcohol septal ablation include older or advanced age, significant comorbidity that selectively increases surgical risk, (eg, significant concerns about lung or airway management), and the patient's strong desire to avoid open heart surgery after a thorough discussion of both options.

9.3.2. Results of Invasive Therapy for the Relief of LVOT Obstruction

More detailed discussions specific to each type of procedure follow in subsequent sections of this document. Overall, reports suggest that technical success, variably defined, is achieved in 90% to 95% of patients who undergo surgical myectomy,²⁷³ less in septal ablation, and only in the minority of patients studied in trials of pacemaker therapy.^{132,134,135,274} Patients undergoing septal ablation may have hemodynamic and symptomatic improvement comparable to septal myectomy if the area of the SAM-septal contact can be accessed by the first septal perforator and ablated. However, compared with septal myectomy in which the hypertrophied muscle is directly visualized and resected, successful septal ablation is dependent on the variable septal artery anatomy, which may not supply the targeted area of the septum in up to 20% to 25% of patients.^{60,275}

In a nonrandomized retrospective evaluation of patients with HCM <65 years of age, survival free from recurrent symptoms favored myectomy over ablation (89% versus 71%, $P=0.01$).⁶⁰ Procedural success is associated with very low mortality (<1% for myectomy,^{64,65,276} ranging from 0% to 4% for ablation),^{277–279} and low nonfatal complication rates (2% to 3% in experienced centers). The exception is high-grade atrioventricular block requiring permanent pacemakers following septal ablation (in 10% to 20% of patients), an inherent aspect of the septal infarction.^{279a–c}

9.3.3. Operator Experience

Operator and institutional experience, including procedural volume, is a key determinant of successful outcomes and lower complication rates for any procedure. For HCM, a disease of substantial heterogeneity and relatively uncommon

in general cardiology practice, this is an important issue. As a consensus opinion, the writing committee recommends an operator volume of at least 20 procedures or that the operator work within the context of an HCM program with a cumulative procedural volume of at least 50 procedures. In addition, given the data available from experienced centers, operators and institutions should aim to achieve mortality rates of <1% and major complication rates of <3%, with documented success in both hemodynamic and symptom benefit for their patients. This is best achieved in the context of a systematic program dedicated to the multidisciplinary and longitudinal care of patients with HCM.

9.3.4. Surgical Therapy

Transaortic septal myectomy is currently considered the most appropriate treatment for the majority of patients with obstructive HCM and severe symptoms unresponsive to medical therapy (Figure 4).^{126,273,280–288} Surgical results, although vastly improved in recent years, are nevertheless limited to relatively few centers with extensive experience and particular interest in the management of HCM.^{270,289} Both the traditional myectomy (Morrow procedure) with about a 3-cm long resection²⁸⁴ or extended myectomy (a resection of about 7 cm) are currently used.^{270,289}

The transaortic approach remains the primary method of exposure. Virtual abolition of the LV outflow gradient and mitral regurgitation is usually accomplished by muscular resection resulting in physical enlargement of the outflow tract and by interruption of the mitral valve SAM, which is usually responsible for the outflow gradient.²⁹⁷

In selected circumstances, some surgeons have also used concomitant mitral valve repair, particularly when the anterior leaflet is elongated. Finally, enlarged or malpositioned papillary muscles can also contribute to residual obstruction. This can be effectively treated by shaving the hypertrophied papillary muscles, incising papillary muscles off the ventricular free wall, and in selected circumstances repositioning one papillary muscle by suture approximation to the adjacent papillary muscle.

9.3.4.1. Outcomes

Early Results. Based on the experience and data assembled from multiple centers worldwide over the last 4 decades,^{126,273,280,282,283,285,286} septal myectomy is established as the most effective and proven approach for reversing the consequences of heart failure by providing amelioration of obstruction (and relief of mitral regurgitation) at rest, with restoration of functional capacity and acceptable quality of life at any age, exceeding that achievable with long-term administration of cardioactive drugs.^{32,290}

LV outflow gradient reduction with myectomy results from basal septal thinning with resultant enlargement of the LVOT area (and redirection of forward flow with loss of the drag and Venturi effects on the mitral valve)²⁹¹ and consequently abolition of SAM and mitral-septal contact.^{289,292,293} Mitral regurgitation is also usually eliminated without the need for additional mitral valve surgery.⁵⁶ With myectomy, left atrial size (and possibly long-term risk for AF) is reduced⁶⁵ and LV pressures (and wall stress) are normalized.^{32,56,64,291,294} Thus, obstructive HCM is a surgically and mechanically reversible form of heart failure. In experi-

enced centers, operative risk is now particularly low, in the range of <1%.²⁹⁰

Late Results. Relief of outflow obstruction by septal myectomy may also extend the longevity of patients with HCM.⁶⁴ Although RCTs involving myectomy surgery have not been performed, in a nonrandomized study, myectomy resulted in excellent long-term survival similar to that in the general population. After septal myectomy, long-term actuarial survival was 99%, 98%, and 95% at 1, 5, and 10 years, respectively (when considering HCM-related mortality). This survival rate did not differ from that expected in a matched general US population and was superior to that achieved by patients with obstructed HCM who did not undergo surgical myectomy.⁶⁴ Similarly the rate of SCD or appropriate ICD discharge after myectomy is very low (<0.9%).^{64,295,296} Nonetheless, surgical myectomy does not eliminate the need to assess each patient's risk for SCD and to consider placement of an ICD in those with a significant risk burden.

9.3.4.2. Complications

Complications following myectomy are rare when performed in experienced centers.²⁹⁷ The risk of complete heart block is approximately 2% with myectomy (higher in myectomy patients with preexisting right bundle-branch block), but in myectomy patients who have had previous alcohol septal ablation, risk is much higher (50% to 85%).²⁹⁸ Iatrogenic ventricular septal defect occurs in <1% of patients.

9.3.4.3. Mitral Valve Abnormalities and Other Anatomic Issues

Abnormalities of the mitral valve and subvalvar apparatus (including anomalous direct anterolateral papillary muscle insertion into anterior mitral leaflet and elongated mitral leaflets)^{224,299} can be identified preoperatively with TTE or intraoperative TEE and can be corrected with modified mitral valve repair or extended myectomy techniques without the need for mitral valve replacement.

9.3.5. Alcohol Septal Ablation

First reported in 1995,²⁶⁶ alcohol septal ablation uses transcatheter administration of absolute ethanol via a percutaneous approach to induce a localized infarction of the basal septum at the point of contact of the anterior mitral valve leaflet, thereby reducing outflow tract gradient and associated mitral regurgitation and simulating the results of surgical myectomy. Developed as an alternative to surgical septal myectomy, the technique is particularly useful when surgery is contraindicated and in patients who are considered poor surgical candidates.¹²⁹ Since its development, alcohol septal ablation has been performed successfully in a large number of patients.⁶²

Contrast angiography of the septal perforator through the balloon central lumen with simultaneous echocardiographic guidance^{300,301} confirms delivery to only the target myocardium. About 1 to 3 mL of alcohol is infused in controlled fashion.^{59,302–304} It is important that the balloon be inflated and that a contrast injection also show that there is no extravasation of dye into the distal left anterior descending coronary artery. Contrast enhancement of other regions (papillary muscles, free wall) indicates collateral circulation from the septal perforator artery, and alcohol should not be infused.

A decrease in resting and provokable gradients usually occurs immediately after the procedure (because of stunning), and remodeling can result in continued or variable gradient reduction over the first 3 months after the procedure.

9.3.5.1. Selection of Patients

Alcohol septal ablation has the potential for greater patient satisfaction because of the absence of a surgical incision and general anesthesia, less overall discomfort, and a much shorter recovery time. The benefit of alcohol septal ablation in patients of advanced age is similar to that in other patients.^{127,305} Because the postoperative risks and complications of cardiac surgery increase with age, ablation may offer a selective advantage in older patients, in whom operative risk may be increased because of comorbidities. Alcohol septal ablation is not indicated in children.

On the other hand, longer-term follow-up data are available for septal myectomy than for septal ablation, a consideration relevant to the selection of patients for either septal reduction therapy. The likelihood of implantation of a permanent pacemaker is 4- to 5-fold higher after septal ablation than after septal myectomy. Furthermore, patients with massive septal thickness approaching or exceeding 30 mm may experience little or no benefit from septal ablation. The surgeon can tailor the myectomy under direct visualization to address specific anatomic abnormalities of the LVOT or mitral valve apparatus, whereas alcohol septal ablation indirectly (and is restricted to) targets the distribution of the septal perforator artery.

Septal myectomy is the preferred treatment option for most severely symptomatic patients with obstructive HCM, especially in younger, healthy adults, whereas septal ablation is preferred in patients for whom surgery is contraindicated or considered high risk (particularly the elderly) (Figure 4). Data comparing alcohol septal ablation with septal myectomy are inadequate to fully inform clinical decision making in certain cases. For such patients, the principle of patient autonomy dictates that it is appropriate for the informed patient to choose between the 2 procedures.

9.3.5.2. Results

Necrosis of the basal ventricular septum³⁰⁶ produces an immediate fall in gradient from decreased septal contraction in >90% of patients.^{66,279,307–309} This effect is followed by LV remodeling over 6 to 12 months, a process that includes scar retraction and resultant widening of the outflow tract, associated with further reduction in gradient and degree of mitral regurgitation, regression of hypertrophy, and improvement in diastolic function.^{63,279,310–312} The beneficial results of alcohol septal ablation have been reported to almost 5 years after the procedure with improved functional and angina classes, exercise capacity, and quality of life.^{62,279,313–316} However, hemodynamic and symptomatic success is dependent on the ability to cannulate and ablate a septal perforator artery that supplies the area of the SAM-septal contact.

Although RCTs comparing surgical myectomy with alcohol septal ablation have not been conducted and are highly unlikely in the future, meta-analyses have noted similar hemodynamic and functional improvement over 3 to 5 years when examining the cumulative average of outcomes.^{317–319}

What the meta-analyses do not report are a subset of patients in whom alcohol septal ablation is unreliable because of the inability to ablate the area of the SAM-septal contact.³²⁰ Older patients, especially those considered to be at high surgical risk, may be well served by alcohol septal ablation, whereas younger patients may benefit most from surgical myectomy.^{60,129} Despite age differences in treatment allocation, with septal ablation patients on average approximately 10 years older in clinical practice,^{317,318} the 4-year survival rate is similar for the 2 procedures.^{60,128} Most studies that have compared surgical myectomy and alcohol septal ablation have involved a large single-center experience in which treatment assignment was not randomized.

9.3.5.3. Complications

In approximately half of patients undergoing alcohol septal ablation, temporary complete atrioventricular block occurs during the procedure.^{321–323} Persistent complete heart block prompting implantation of a permanent pacemaker occurs in 10% to 20% of patients based on the available data.³⁶ Approximately 5% of patients have sustained ventricular tachyarrhythmias during hospitalization. The in-hospital mortality rate is up to 2%.^{60,62,129,318} Because of the potential for creating a ventricular septal defect, septal ablation should not be performed if the target septal thickness is ≤ 15 mm.

Alcohol septal ablation is a therapeutic alternative to surgical myectomy for selected patients and produces a transmural infarction of ventricular septum occupying on average 10% of the overall LV wall.^{144,275,324} There has been concern that the potential ventricular arrhythmogenicity of the scar created by septal ablation might augment risk in the HCM population. Several studies have documented the occurrence of sustained ventricular arrhythmias^{301,314,325–331} and SCD following septal ablation²⁹⁶ in about 3% to 10% of patients both with or without risk factors for SCD. Patients with HCM considered to carry sufficient risk to warrant ICD placement have an annual incidence of appropriate interventions for VT/ventricular fibrillation of 3% to 10%.^{150,328,332} It is uncertain how common such events are attributable to the procedure or alternatively to the underlying disease, but the incidence of sustained ventricular arrhythmias after myectomy is extremely low (0.2% to 0.9% per year).^{64,295,296}

Meta-analyses have indicated no difference between septal ablation and myectomy in the medium-term incidence of SCD or all-cause mortality.^{317,333} Although no definitive evidence is available that the ablation scar as such increases (or does not increase) long-term risk for SCD in absolute terms in this patient population, resolution will require greatly extended follow-up studies in larger patient cohorts.^{144,325}

9.3.6. DDD Pacing

Implantation of a dual-chamber pacemaker was proposed as an alternative treatment for patients with severe symptomatic obstructive HCM.^{335–337} However, there have been 3 randomized crossover trials showing that although symptomatic improvement was reported by the majority of patients following continuous DDD pacing, a similar frequency of improvement was reported by patients during the AAI mode (control mode without pacing). These findings suggest a

placebo effect responsible for the perceived improvement in symptoms.^{136,137,338} However, there is some evidence that patients >65 years of age may be a subgroup who achieve the greatest benefit.¹³⁶ There are no data that dual-chamber pacing either reduces the risk of SCD in patients with HCM, alters the underlying progression of disease, or is of benefit to patients with nonobstructive HCM.^{136,335,339} A trial of dual-chamber pacing may be considered for symptomatic patients with obstruction in whom an ICD has already been implanted for high-risk status.

9.3.7. LV Systolic Dysfunction

Standard heart failure therapies should be implemented in patients with HCM when EF is $\leq 50\%$. Patients with HCM were not included in the primary prevention ICD trials for patients with heart failure due to CAD or dilated cardiomyopathy (and reduced EF). Prophylactic ICD implantation is nevertheless the generally accepted clinical practice for HCM patients with systolic dysfunction.

9.4. Prevention of SCD

A minority of clinically recognized patients with HCM are judged to be at increased risk for SCD, with a rate of about 1% per year.^{143–146,148,150} ICDs offer the only effective means of preventing SCD and prolonging life in patients with HCM.¹⁵⁰ Selection of patients who are appropriate for implantation for primary as opposed to secondary prevention can be a difficult clinical decision owing to the individuality of each patient and family, variable definitions for risk markers, sparse clinical data, the relative infrequency of both HCM and SCD in most clinical practices, and the cumulative morbidity of living with an ICD.

9.4.1. Established Risk Markers

9.4.1.1. Prior Personal History of Ventricular Fibrillation, SCD, or Sustained VT

As expected, patients with HCM who have experienced SCD or sustained VT represent the highest risk for subsequent arrhythmogenic events. The annualized rate of subsequent events is approximately 10% per year, although it has been shown that individuals may have no recurrent events or may have decades-long arrhythmia-free intervals between episodes.^{145,146,148,150,340}

9.4.1.2. Family History of SCD

It has been recognized that SCD events can cluster in families. Notably, some studies have not demonstrated an independent link between family history of SCD and risk for individual patients on multivariate analysis,^{147,149,155} whereas others have suggested that family history is an independent predictor.¹⁵⁵ These differences may be explained in part by the relative infrequency of events but also likely reflect variability in the definition of a family history of SCD.

9.4.1.3. Syncope

Syncope represents a complex symptom with a multifactorial etiology that requires a careful clinical history before it can be considered a potential marker for SCD.^{147,152} In one analysis, syncope that was unexplained or thought to be consistent with arrhythmia (ie, not neurally mediated) showed a significant

independent association with SCD only when the events occurred in the recent past (<6 months).¹⁵²

9.4.1.4. Nonsustained Ventricular Tachycardia

Although sustained ventricular arrhythmia is clearly associated with SCD, the data for NSVT are less robust. However, 1 contemporary study showed that NSVT is independently associated with SCD on multivariate analysis³⁰ and is more important in younger patients (<30 years of age).³³ Furthermore, exercise-induced NSVT has been found to have independent association with SCD.³⁴¹ NSVT probably should not be considered in a simply binary manner (ie, as either positive or negative), and there may be some value in long-term ambulatory monitoring when NSVT is discovered on the screening 24-hour assessment.

9.4.1.5. Maximum LV Wall Thickness

The relationship between severity of LV hypertrophy and SCD has been investigated in several studies predicated on the concept that the more severe the disease expression, the more likely the individual patient is to experience adverse events. Most, but not all,^{156,342} studies have shown at least a univariate association between maximum wall thickness and SCD,^{148,342,343} whereas other large studies have shown that when magnitude of hypertrophy is ≥ 30 mm, there is an independent association with SCD.^{147,152,158}

9.4.1.6. Abnormal Blood Pressure Response During Exercise

For up to a third of patients with HCM, there is an inappropriate systemic systolic blood pressure response during exercise testing (defined as either a failure to increase by at least 20 mm Hg or a drop of at least 20 mm Hg during effort).^{70,71} Two studies have shown a univariate association between this finding and subsequent SCD.^{30,71,147,149}

9.4.2. Other Potential SCD Risk Modifiers

9.4.2.1. LVOT Obstruction

Although some studies have not found a significant association between LVOT obstruction and SCD,^{51,158,212} other studies have found higher rates of SCD among patients with resting gradients ≥ 30 mm Hg^{30,149} and that the risk is positively correlated with severity of LVOT obstruction.³⁰ Conversely, relief of outflow tract obstruction through surgical myectomy is associated with very low rates of SCD.^{64,307} A limitation to using LVOT obstruction as an independent risk marker is that the obstruction in HCM is dynamic and highly variable.^{225,344}

9.4.2.2. LGE on CMR Imaging

There has been considerable interest in promoting LGE on CMR imaging as a potential SCD risk marker in HCM. Because LGE is believed to represent myocardial fibrosis or scarring, it has been hypothesized that LGE may represent myocardium prone to ventricular tachyarrhythmia.⁸² Indeed, LGE has been associated with NSVT and ventricular ectopy but has not been associated with clinical SCD events or ICD discharge in published studies.^{78,79,82} More recent studies have shown a relationship between LGE and SCD and heart failure, but with low positive predictive accuracy.^{80,81}

9.4.2.3. LV Apical Aneurysm

A subset of patients with HCM (prevalence about 2%) develop a thin-walled LV apical aneurysm associated with regional scarring⁷⁵ and more adverse clinical events during follow-up, including progressive heart failure and evolution into the end-stage phase, as well as SCD. Although data on LV aneurysms in HCM are limited, this abnormality may warrant consideration in SCD risk-assessment strategies.

9.4.2.4. Genetic Mutations

SCD may cluster in certain families with HCM, and the possibility that specific sarcomere mutations may confer SCD risk has been hypothesized. Indeed, several early studies of HCM pedigrees implicated certain mutations as “malignant.”^{20,227,345,346} However, subsequent studies of less selected consecutive patients with HCM found that it was problematic to infer likelihood of SCD events on the basis of the proposed mutations, because in some instances the rate of adverse events (and prevalence of associated SCD risk markers) was lower in patients with “malignant” mutations than it was in those with mutations believed to be “benign.”^{8,347–349} The data from unselected consecutive outpatients suggest that most mutations are “novel” and limited to particular families (“private” mutations). Therefore, routine mutational screening would appear to be of little prognostic value in HCM.

9.4.3. Utility of SCD Risk Markers in Clinical Practice

Other than cardiac arrest, each of the HCM risk factors has low positive predictive value (approximately 10% to 20%) and modestly high negative predictive value (85% to 95%). Multiple risk markers in individual patients would intuitively suggest greater risk for SCD; however, the vast majority of patients with ≥ 1 risk marker will not experience SCD, and simple arithmetic summing of risk markers is not precise because of the uncertainty implicit in assigning a relative weight to any individual risk factor.^{147,156,350} Notably, in the international HCM-ICD registry,¹⁵⁰ the number of risk factors did not correlate with the rate of subsequent appropriate ICD discharges among presumably high-risk patients selected for ICD placement. These data suggest that the presence of a single risk marker may be sufficient to warrant ICD placement in many patients, but these decisions need to be individualized with respect to age, the strength of the risk factor, and the risk-benefit of lifelong ICD therapy.^{150,351}

9.5. ICD Therapy in HCM

Although the overall rate of SCD in HCM is approximately 1% per year, clearly there are individuals at higher risk for whom prophylactic therapy may be indicated. Pharmacologic therapy has not been demonstrated to provide protection from SCD. Conversely, the ICD has proved to be effective in terminating life-threatening ventricular tachyarrhythmia in HCM, altering the natural course of the disease and prolonging life.

The decision for placement of primary prevention ICD in HCM often involves a large measure of individual clinical judgment, particularly when the evidence for risk is ambiguous. The potential for SCD needs to be discussed with each fully informed HCM patient and family member in the

context of their concerns and anxieties and should be balanced against the risks and benefits of proposed prophylactic ICD strategy. Consideration of the patient's age is warranted, particularly because device complications are more likely in children and young adults over the long period of follow-up.^{150,351}

There have been 2 reports from an international, multi-center registry of patients with HCM who have undergone ICD placement on the basis of the clinical perception of SCD sufficient to justify device therapy.^{150,153} Among patients who received a device as a result of a prior personal history of cardiac arrest or sustained ventricular arrhythmia (secondary prevention ICD), the annualized rate of subsequent appropriate ICD discharge was 10% per year. Patients with primary prevention ICDs placed on the basis of 1 or more of the conventional risk markers experienced appropriate ICD therapy at a rate of 4% per year.^{150,153} The number of risk markers present did not predict subsequent device discharge.^{150,351}

9.5.1. Complications of ICD Therapy in HCM

It is important to recognize and discuss with patients potential ICD-related complications (both procedural and long term) that occur at a rate of 4% per year in patients with HCM.³⁵¹ Potential early problems may include pneumothorax, pericardial effusion, pocket hematoma, acute pocket infection, and/or lead dislodgment. Late complications include upper extremity deep venous thrombosis, lead dislodgment, infection, high defibrillation threshold necessitating lead revision, and inappropriate shocks, that is, shocks triggered by supraventricular arrhythmias, sinus tachycardia, lead fractures or dislodgment, oversensing, double counting, and programming malfunctions.

Reported rates of complications include approximately 25% of patients with HCM who experienced inappropriate ICD discharge; 6% to 13% who experienced lead complications (fracture, dislodgment, oversensing); 4% to 5% who developed a device-related infection; and approximately 2% to 3% who experienced bleeding or thrombosis complications.^{150,351} The rate of inappropriate shocks and lead fractures appears to be higher in children than in adults, largely because their activity level and body growth places continual strain on the leads, which are the weakest link in the system.¹⁴³ ICD leads fail at a rate of 0.5% to 1% per year, although there are data showing that failure rates are increased in younger populations.¹⁶⁰ This issue is of particular concern, given the long periods that young patients will have prophylactically implanted devices.

Industry-related ICD problems have affected patients with HCM. Prominent recalls have included defective generators leading to several deaths³⁵² and small-diameter high-voltage leads prone to fracture.^{160,353} The implant procedure has been largely free of significant risk, without reported deaths, although selected patients with extreme hypertrophy or who have received amiodarone may require high-energy output generators or epicardial lead systems.³⁵⁴

In patients with LVOT obstruction in whom ICDs are indicated, dual-chamber pacing may have the potential to reduce gradient and symptoms (Section 2.10). In general, the younger the patient, the more appropriate it is for single-

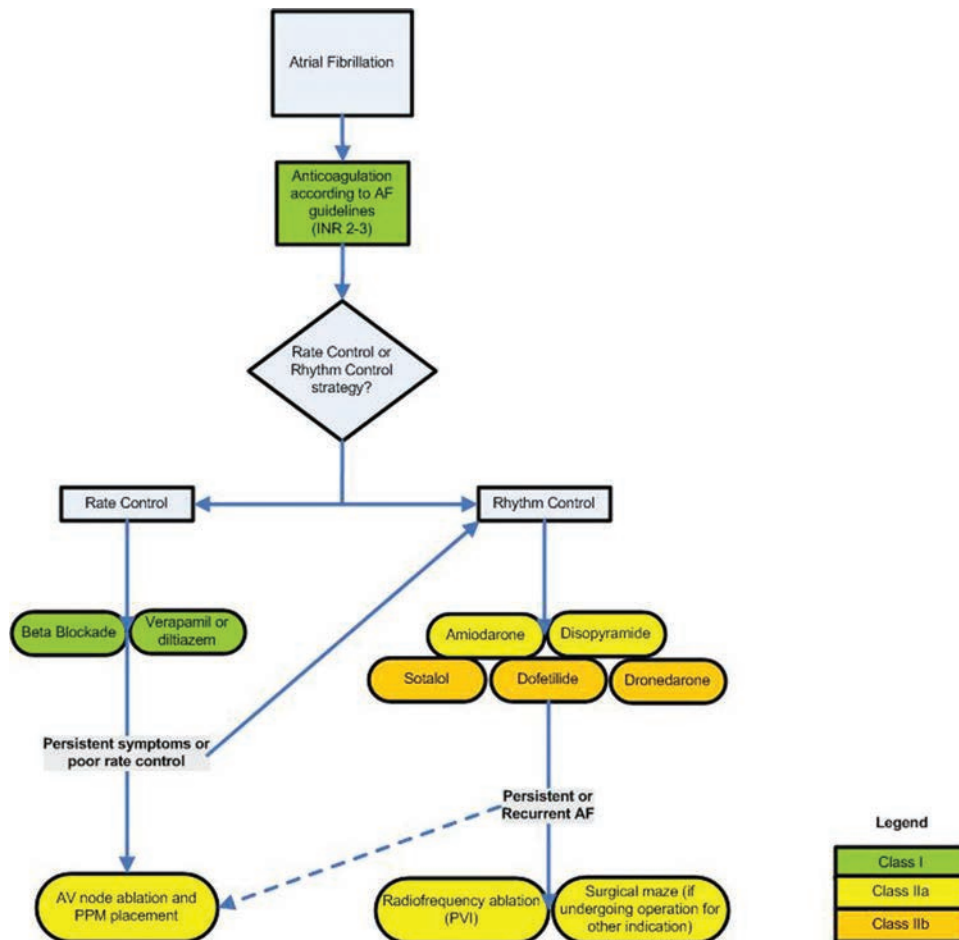


Figure 5. Management of AF in HCM. AF indicates atrial fibrillation; AV, atrioventricular; INR, international normalized ratio; PPM, permanent pacemaker; and PVI, pulmonary vein isolation.

chamber devices to be used to decrease the amount of hardware in the venous system.

9.6. Participation in Competitive or Recreational Sports and Physical Activity

A number of large cohort studies from the United States indicate that HCM is the most common cardiovascular cause of SCD in young athletes, accounting for about one third of these events.^{166–168,355} The American College of Cardiology Bethesda Conference No. 36,^{163,339} as well as the European Society of Cardiology guidelines^{164,356} indicate that risk for SCD is increased during intense competitive sports and also suggest that the removal of these individuals from the athletic arena can diminish their risk. This principle is the basis for disqualification of athletes with HCM from sanctioned high school and college sports.^{163,356} It should be underscored that these consensus recommendations for competitive athletes are independent of those for noncompetitive, informal recreational sporting activities.⁸⁷

General recommendations for recreational exercise in patients with HCM should be tailored to the individual's desires and abilities; however, certain guidelines prevail. For example, aerobic exercise as opposed to isometric exercise is preferable. Patients with HCM should avoid recreational sports in which participation is intense and simulates com-

petitive organized athletics. Also, burst exertion, in which an abrupt increase in heart rate is triggered (eg, sprinting in half-court basketball), is less desirable than swimming laps or cycling. Finally, it is prudent for such patients to avoid physical activity in extreme environmental conditions of heat, cold, or high humidity, with attention paid to maintaining volume status. Detailed recommendations for individual sports appear in Table 2.

9.7. Atrial Fibrillation

AF is an important cause of symptoms, morbidity, and even mortality in patients with HCM.^{50,172} Patients with HCM are at increased risk of AF compared with age-matched cohorts, but AF is seldom seen in patients with HCM who are <30 years of age and becomes more prevalent with age. AF occurring in HCM may not be associated with symptoms or hemodynamic compromise in one third of patients but is poorly tolerated in many others. There is evidence that AF is an indicator of unfavorable prognosis, including increased risk of HCM-related heart failure, death, and stroke.^{172,357}

Therapy for AF includes prevention of thromboembolic stroke and controlling symptoms (Figure 5). The risk of systemic embolization is high in patients with HCM with AF but is not related to the severity of symptoms.^{50,172} Occurrence of paroxysmal, persistent, or chronic AF is a strong

indication for anticoagulation with a vitamin K antagonist.¹⁷⁰ Whether there is a threshold for AF that warrants anticoagulation is unresolved; however, given the high risk of thromboembolism in HCM, even patients with short episodes of AF should be strongly considered for anticoagulation. Aspirin should be reserved for those who cannot or will not take warfarin or other oral anticoagulants, but its efficacy in HCM is unestablished.

Symptom control may be attained with adequate rate control, although many patients will require rhythm control. Rate control is best maintained by beta blockers and calcium channel blockers. High doses of these agents may be required. Digoxin may modestly reduce ventricular rate at rest and to a lesser extent with exertion. Because there is a paucity of data on rhythm control in patients with HCM, evidence from other patient populations is extrapolated to HCM. However, whether patients with HCM respond similarly to antiarrhythmic agents is not clear. The “2011 ACCF/AHA/HRS Focused Updates Incorporated Into the ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation” state that disopyramide and amiodarone are potential agents for rhythm control.¹⁷⁰ The limited published data on amiodarone suggest that it is safe and effective for patients with HCM.^{358–361} Disopyramide has been shown to be safe when prescribed for reduction of LVOT obstruction, but its safety and efficacy in AF are not well established.^{68,362} Dronedarone, an antiarrhythmic agent similar to amiodarone but lacking the iodine moiety and much of the long-term toxicity, has been approved for use in the United States. There are no data regarding the efficacy of dronedarone or the use of flecainide and propafenone in patients with HCM. The management of atrial flutter in HCM is similar to that in other disease states, including the role of radiofrequency ablation.

The long-term benefits of radiofrequency ablation versus antiarrhythmic drugs in patients with HCM remain to be established. It does appear that early success and complication rates are similar between HCM and other forms of heart disease or absence of heart disease.^{175,178,179,363} The surgical maze procedure for AF has shown some limited success³⁶⁴; however, whether a prophylactic or therapeutic surgical maze procedure is indicated for patients undergoing other open chest surgical procedures (ie, septal myectomy) is unresolved.

10. Occupational Considerations

In 2002, the US Department of Transportation Federal Motor Carrier Safety Administration published its “Cardiovascular Advisory Panel Guidelines for the Medical Examination of Commercial Motor Vehicle Drivers.” The guidelines state that “irrespective of symptoms, a person should not be certified as a [commercial motor vehicle] driver if a firm diagnosis of [HCM] is made”^{365(p83)} Although consider-

ation has subsequently been given to liberalizing this restriction, the guidelines have not yet been revised.

The criteria for the disqualification of aircraft pilots with cardiovascular disease are set by the Federal Aviation Administration. Currently, HCM is regarded as generally incompatible with the highest grade aviation license for commercial pilots, based on the unpredictable risk for impairment in the cockpit attributable to HCM.³⁶⁷

Staff

American College of Cardiology Foundation

David R. Holmes, Jr, MD, FACC, President

John C. Lewin, MD, Chief Executive Officer

Janet Wright, MD, FACC, Senior Vice President, Science and Quality

Charlene May, Senior Director, Science and Clinical Policy

American College of Cardiology Foundation/American Heart Association

Lisa Bradfield, CAE, Director, Science and Clinical Policy

Sue Keller, BSN, MPH, Senior Specialist, Evidence-Based Medicine

Jesse M. Welsh, Specialist, Science and Clinical Policy

American Heart Association

Ralph L. Sacco, MS, MD, FAAN, FAHA, President

Nancy Brown, Chief Executive Officer

Rose Marie Robertson, MD, FAHA, Chief Science Officer

Gayle R. Whitman, PhD, RN, FAHA, FAAN, Senior Vice President, Office of Science Operations

Mark D. Stewart, MPH, Science and Medicine Advisor, Office of Science Operations

Jody Hundley, Production Manager, Scientific Publications, Office of Science Operations

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||The Federal Motor Carrier Safety Administration defines *commercial motor vehicle* as a motor vehicle or combination of motor vehicles used in commerce to transport passengers or property if the motor vehicle:

(a) has a gross combination weight rating of $\geq 11\,794$ kg ($\geq 26\,001$ lb) inclusive of a towed unit(s) with a gross vehicle weight rating of $\geq 4\,536$ kg (10 000 lb); or
 (b) has a gross vehicle weight rating of $\geq 11\,794$ kg ($\geq 26\,001$ lb); or
 (c) is designed to transport ≥ 16 passengers, including the driver; or
 (d) is of any size and is used in the transportation of hazardous materials as defined [by the Federal Motor Carrier Safety Administration].³⁶⁶

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KEY WORDS: AHA Scientific Statements ■ ablation ■ cardiomyopathy, hypertrophic ■ defibrillators, implantable ■ hypertrophy ■ myocardial disease ■ surgical procedures, operative

Appendix 1. Author Relationships With Industry and Other Entities (Relevant)—2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy

Committee Member	Employer/Title	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section Number*
Bernard J. Gersh, Co-Chair	Mayo Clinic—Professor of Medicine	● Abbott Laboratories† ● AstraZeneca ● Boston Scientific ● Bristol-Myers Squibb	None	None	● Amocyte (DSMB)	● CV Therapeutics	None	6.2.2.6 6.2.3 6.3.2 6.3.2.4
Barry J. Maron, Co-Chair	Minneapolis Heart Institute Foundation—Director, Hypertrophic Cardiomyopathy Center	● GeneDx‡	None	None	● Medtronic‡	None	None	5.1 6.3.2 6.3.2.4
Robert O. Bonow	Northwestern University Feinberg School of Medicine—Goldberg Distinguished Professor of Medicine; Chief, Division of Cardiology	None	None	None	None	None	None	None
Joseph A. Dearani	Mayo Clinic—Professor of Surgery	None	None	None	None	None	None	None
Michael A. Fifer	Massachusetts General Hospital—Director, Hypertrophic Cardiomyopathy Program	None	None	None	● Merck‡	None	None	6.2.1
Mark S. Link	Tufts Medical Center—Professor of Medicine	None	● Medtronic ● Guidant	None	● Guidant	None	● Plaintiff, wrongful death secondary electrocution, 2007–2009 ● Defendant, postoperative valve replacement management, 2007–2010	6.2.2.6 6.3.2 6.3.2.4
Srihari S. Naidu	Winthrop University Hospital—Director, Cardiac Catheterization Laboratory; Director, Hypertrophic Cardiomyopathy Center	None	● Abbott Vascular ● Cordis ● Medtronic	None	None	None	None	6.2.2.6 6.3.2 6.3.2.4
Rick A. Nishimura	Mayo Clinic—Consultant in Cardiology	None	None	None	None	None	None	None
Steve R. Ommen	Mayo Clinic—Professor of Medicine	None	None	None	None	None	None	None
Harry Rakowski	Toronto General Hospital, University Health Network—Director, Hypertrophic Cardiomyopathy Center; Wight Chair for HCM Research; Professor of Medicine, University of Toronto	None	None	None	● Medtronic Valve Device (DSMB)	None	None	None
Christine E. Seidman	Howard Hughes Medical Institute; Harvard Medical School/Brigham and Women's Hospital—Investigator; T.W. Smith Professor of Medicine and Genetics	None	None	None	None	None	None	None
Jeffrey A. Towbin	Cincinnati Children's Hospital—Executive Co-Director, The Heart Institute; Professor and Chief, Pediatric Cardiology	None	None	None	None	None	None	None
James E. Udelson	Tufts Medical Center—Chief, Division of Cardiology	None	None	None	None	None	None	None
Clyde W. Yancy	Baylor University Medical Center—Medical Director	None	None	None	None	None	None	None

This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of $\geq 5\%$ of the voting stock or share of the business entity, or ownership of $\geq \$10\,000$ of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

*Writing committee members are required to recuse themselves from voting on sections where their specific relationships with industry may apply. Section numbers apply to the full-text guideline.

†No financial benefit.

‡Significant relationship.

DSMB indicates data safety monitoring board.

Appendix 2. Reviewer Relationships With Industry and Other Entities (Relevant)—2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy

Peer Reviewer	Representation	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
David R. Holmes, Jr	Official Reviewer—ACCF Board of Governors/ACCF Interventional Scientific Council	None	None	None	None	None	None
William J. McKenna	Official Reviewer—AHA	None	None	None	None	None	None
William G. Stevenson	Official Reviewer—ACCF/AHA Task Force on Practice Guidelines	None	None	None	None	None	None
Carole A. Warnes	Official Reviewer—ACCF Board of Trustees	None	None	None	None	None	None
Michael Argenziano	Organizational Reviewer—AATS	None	None	None	None	None	None
Drew E. Baldwin	Organizational Reviewer—SCAI	None	None	None	● Atrium† ● GlaxoSmithWellcome† ● Harvard Clinical Research Institute†	● Greater New Orleans Health Services Corps*	None
Hugh Calkins	Organizational Reviewer—HRS	● Medtronic	● Boston Scientific	None	● Boston Scientific* ● Medtronic* ● St. Jude Medical*	None	None
Milind Y. Desai	Organizational Reviewer—ASNC	None	None	None	None	None	None
Vasken Dilsizian	Organizational Reviewer—ASNC	None	None	None	None	None	None
N.A. Mark Estes III	Organizational Reviewer—HRS	● Boston Scientific*	None	None	None	None	None
Michael Givertz	Organizational Reviewer—HFSA	None	None	None	None	None	None
Stuart Katz	Organizational Reviewer—HFSA	● Amgen ● Bristol-Myers Squibb ● Paracor ● Terumo	● Otsuka	None	None	None	None
John A. Kern	Organizational Reviewer—AATS	None	None	None	None	None	None
Sherif Nagueh	Organizational Reviewer—ASE	None	None	None	None	None	None
Paul Sorajja	Organizational Reviewer—SCAI	None	None	None	None	None	None
Kirk T. Spencer	Organizational Reviewer—ASE	None	None	None	None	None	None
Gus J. Vlahakes	Organizational Reviewer—STS	None	None	None	None	None	None
Herbert B. Ward	Organizational Reviewer—STS	None	None	None	None	None	None
Nancy M. Albert	Content Reviewer—ACCF/AHA Task Force on Practice Guidelines	None	None	None	None	None	None
Jeffrey L. Anderson	Content Reviewer—ACCF/AHA Task Force on Practice Guidelines	None	None	None	● AstraZeneca (DSMB) ● Toshiba	None	None
Richard G. Bach	Content Reviewer	None	None	None	None	None	None
Jorge A. Belardi	Content Reviewer—ACCF Interventional Scientific Council	● Boston Scientific ● Medtronic CardioVascular ● Medtronic Vascular	● Abbott ● Boston Scientific	None	None	None	None
Eugene Braunwald	Content Reviewer	None	None	None	None	None	None
John E. Brush, Jr	Content Reviewer	● Prometheus Payment† ● United Healthcare	None	None	None	None	None
James A. Burke	Content Reviewer—ACCF Interventional Scientific Council	None	None	None	None	None	None
Jose G. Diez	Content Reviewer—ACCF Interventional Scientific Council	● Sanofi-aventis	● Sanofi-aventis	None	None	None	None
Jon C. George	Content Reviewer—ACCF Interventional Scientific Council	None	None	None	None	None	None
Robert A. Guyton	Content Reviewer—ACCF/AHA Task Force on Practice Guidelines	None	None	None	None	None	None
Judith S. Hochman	Content Reviewer—ACCF/AHA Task Force on Practice Guidelines	● GlaxoSmithKline	None	None	None	None	None

(Continued)

Appendix 2. Continued

Peer Reviewer	Representation	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Frederick G. Kushner	Content Reviewer—ACCF/AHA Task Force on Practice Guidelines	None	None	None	None	None	None
Gilead I. Lancaster	Content Reviewer—ACCF Board of Governors	None	None	● Cardiogal	None	None	None
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Gary D. Webb	Content Reviewer—ACCF Adult Congenital and Pediatric Cardiology Council	None	None	None	None	None	None
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AATS indicates American Association for Thoracic Surgery; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; ASE, American Society of Echocardiography; ASNC, American Society of Nuclear Cardiology; DSMB, data safety monitoring board; HFSA, Heart Failure Society of America; HRS, Heart Rhythm Society; SCAI, Society for Cardiovascular Angiography and Interventions; and STS, Society of Thoracic Surgeons.

2011 HCM Guideline Data Supplements

Data Supplement 1. Genetics Table

Study Name/Author (Citation)	Aim of Study	Study Design	Study Size	Patient Population	Endpoints	Results	Comments
Quality of life and psychological distress in HCM mutation carriers: a cross-sectional cohort study Christiaans, et al. (1)	To determine the quality of life and psychological distress in HCM mutation carriers.	Cross sectional cohort study	228 pts who underwent genetic testing for HCM mutation	Carriers of HCM mutations. 49.1% men, 88.7% with children. Study group divided between those with known HCM and those with unknown clinical status, in whom genotype would be predictive (n=123). Among those with predictive genotype: 43% were men and 57% were women, with 76.4% had children.	Quality of life and psychological distress assessed. Mutation carrier responses were compared to the general population.	Overall scores of quality of life were not different from the general population. Among those with overt HCM, quality of life and distress were worst than general population. Predictive genetic testing did not cause worse psychological test scores than those in the general population. Among those whose DNA testing indicated they did not carry a HCM mutation, quality of life scores were better than general population.	This was the first study to show that there was no psychologic harm caused by predictive genetic testing in HCM.
Characteristics and prognostic implications of myosin missense mutations in familial HCM Watkins H, et al. (2)	To assess the role of MYH7 mutations in unrelated families with HCM	Genetic analyses of MYH7	25 unrelated HCM probands and ~250 family members	Familial HCM of European descent.	Identification of pathogenic mutations.	Dominant missense mutations in MYH7 accounted for HCM in 12/25 families, indicating this gene accounts for ~50% of familial HCM. Mutations allowed identification of individuals at risk for developing HCM. Different mutations did not appreciably alter the clinical manifestations of familial HCM.	Different missense mutations in the β cardiac myosin heavy-chain gene can be identified in ~50% of families with HCM. The study authors suggest the precise definition of the disease-causing mutation can provide important prognostic information about affected members.
Comprehensive analysis of the beta-myosin heavy chain gene in 389 unrelated pts with HCM Van Driest SL, et al. (3)	Assessment of the prevalence of MYH7 mutations in an unselected HCM cohort	DNA sequence analyses	389 HCM pts	Unrelated HCM pts with familial or sporadic disease referred to a tertiary center.	Identification of pathogenic mutations.	58 pts (15%) had 40 different mutations in MYH7 . HCM pts with MYH7 compared to HCM pts without MYH7 mutations, were younger at diagnosis (32.9 vs. 42.7 years, respectively, p=0.0002), had more hypertrophy (LV wall thickness of 24.2 vs. 21.1 mm, respectively, p=.0009), and more frequently underwent myectomy (60% vs. 38%, respectively, p=0.002). HCM pts with MYH7 mutations compared to HCM pts without MYH7 mutations more often had a family history of HCM	Mutations were identified using indirect methods that are less sensitive than contemporary approaches, such as DNA sequencing. This is likely to account for the lower prevalence of MYH7 mutations than is currently found by contemporary clinical and research mutation tests.

						(43% vs. 29%, respectively, p=.006).	
Mutations in the genes for cardiac troponin T and alpha-tropomyosin in HCM Watkins H, et al. (4)	To determine the role of troponin T and alpha-tropomyosin mutations in HCM	DNA sequence analyses	127 unrelated HCM probands	Probands with familial HCM included 14 from Europe, 10 from North America and 1 each from South America, Africa and India. 100 HCM probands without family histories had diverse racial and ethnic origins.	Identification of pathogenic mutations and clinical status of mutation carriers.	Dominant mutations in cardiac troponin T account for ~15% of familial HCM; dominant mutations in alpha-tropomyosin account for ~3% of HCM.	The high detection rate of troponin T mutations may be due to the referral-center population studied. Subsequent analyses indicate troponin T mutations account for somewhat less (10%) of HCM.
Mutations in the gene for cardiac myosin-binding protein C and late-onset familial HCM Niimura H, et al. (5)	To determine the spectrum of myosin binding protein C mutations and associated clinical features	DNA Sequence analyses	Unrelated HCM probands and 574 family members	Single center analyses of familial HCM.	Identification of pathogenic mutations and clinical status of mutation carriers.	Dominant missense and truncation mutations in cardiac myosin binding protein C account for ~50% of familial HCM. Only 58% of adults age <50 y with a cardiac myosin-binding protein C mutation had clinical manifestations of HCM. Disease penetrance remained incomplete through the age of 60 y.	This was the first study to show myosin binding protein C mutations can delay clinical expression of HCM. This study was significant in that clinical evaluations of family members at risk for HCM must continue throughout life, unless genetic status is ascertained.
Sporadic HCM due to de novo myosin mutations Watkins H, et al. (6)	To determine if isolated cases of HCM, like familial HCM are due to gene mutations.	Single center cohort genetic study	7 pts	Unrelated pts with sporadic HCM.	Identification of pathogenic mutations.	Mutations in the beta cardiac MHC gene were identified in 2 probands with sporadic disease. In each case, the parents were neither clinically nor genetically affected; indicating mutations arose de novo. Transmission of the mutation and disease to an offspring occurred in 1 pedigree, predicting these are germline mutations.	This study demonstrated de novo mutations account for some instances of sporadic HCM and these mutations can be transmitted to children, indicating genetic testing is warranted in pts with sporadic disease.
Shared genetic causes of cardiac hypertrophy in children and adults Morita H, et al. (7)	To determine if idiopathic cardiac hypertrophy in childhood that occurs without a family history of cardiomyopathy has a shared genetic etiology with HCM.	Genetic study of children with idiopathic hypertrophy	84 pts	63 boys/ 21 girls diagnosed before age 15 y (mean [+/-SD], 6.99+/-6.12 y).	Identification of pathogenic mutations and assessment of mutation in family members.	Pathogenic mutations were identified 25 of 51 affected children without family histories of cardiomyopathy and in 21 of 33 affected children with familial HCM. Among 11 of the 25 children with presumed sporadic disease, 4 cases had new mutations and 7 cases had unrecognized inherited mutations.	This study showed mutations in HCM genes account for ~50% of cases of pediatric onset of idiopathic hypertrophy, despite substantially different clinical presentation. In 1/3 of cases, de novo mutations were found. Genetic testing of childhood-onset hypertrophy can help define cause and aid in family evaluations.

Glycogen storage diseases presenting as HCM Arad M, et al. (8)	To determine the genetic causes of HCM with atypical features.	Cohort genetic study of pts with atypical HCM	55 pts	Unrelated HCM pts with massive hypertrophy, early presentation, absent family history, or concurrent electrophysiologic abnormalities.	Identification of pathogenic mutations and assessment of clinical features associated with different genotypes.	Mutations in LAMP2 and PRKAG2 cause hypertrophy with additional features. Clinical features associated with PRKAG2 mutations included electrophysiological abnormalities (pre-excitation and progressive conduction system disease). Clinical manifestations of LAMP2 mutations included male sex, severe hypertrophy, early onset (at age 8 to 17 y), ventricular preexcitation, and asymptomatic elevations of 2 serum proteins.	This study showed that LAMP2 or PRKAG2 mutations resembles HCM but are distinguished by electrophysiological abnormalities, and for LAMP2 mutations, extra- cardiac manifestations. The clinical courses associated with these mutations are distinct from HCM. Gene-based diagnosis can distinguish between HCM and these disorders. This information is helpful to counsel pts and to devise appropriate management strategies.
Preclinical diagnosis of familial HCM by genetic analysis of blood lymphocytes Rosenzweig A, et al. (9)	To determine if genetic information identifies mutation carriers and to define preclinical manifestations of HCM.	Single center family study	29 family members of index HCM patient	15 adult family members and 14 offspring (ages 1- 20 y).	Definition of genotype and clinical features of all study subjects.	In 15 adult relatives there was perfect agreement between genotype and the clinical diagnosis (8 affected and 7 not affected). Clinical analysis of the 14 offspring of affected adults identified 1 child with echocardiographic findings diagnostic of HCM. However, genetic analyses showed 6 other children had also inherited the mutation. Some genotype positive children without LVH had EKG abnormalities, indicating that electrophysiologic manifestations precede LVH in HCM.	This study shows that knowledge of the genetic cause for HCM in an index patient allows preclinical diagnosis of mutation carriers, and identification of relatives who have no risk of developing HCM. Genotype information can precisely define individuals who warrant serial clinical evaluations for HCM.
Assessment of diastolic function with Doppler tissue imaging to predict genotype in preclinical HCM Ho CY, et al. (10)	To determine the preclinical phenotypes in carries of HCM mutations who do not exhibit LVH.	Cohort study	72 pts	36 subjects with HCM mutations; 18 without LVH (genotype+/LVH-) and 18 with LVH (genotype+/LVH+). Controls = 36 age/gender matched individuals without an HCM mutation.	LV function using 2-D echocardiography with Doppler tissue imaging.	LVEF was significantly higher in both genotype (+) groups vs. control subjects. Mean early diastolic myocardial velocities (Ea) were significantly lower in both genotype (+) subgroups, irrespective of LVH.	This study defines the earliest clinical manifestations of HCM. Abnormalities of diastolic function were shown to precede the development of LVH in individuals with HCM mutations. This finding supports the rationale for serial evaluation of genotype + individuals, to enable early detection of the emergence of HCM.

A DNA resequencing array for pathogenic mutation detection in HCM Fokstuen S, et al. (11)	To define gene mutations in familial and sporadic HCM using contemporary sequencing techniques.	Cohort study from a single center	38 pts	17 index pts with familial HCM; 21 with sporadic HCM.	12 genes clearly implicated in HCM were sequenced in all pts. (Genes = MYH7, MYBPC3, TNNT2, TPM1, TNNI3, MYL3, MYL2, CSRP3, PLN, ACTC, TNNC1, and PRKAG2).	Pathogenic mutations were identified in 60% (10/17) of familial HCM and 10% of sporadic cases (2/21).	Contemporary DNA sequencing strategies can detect HCM mutations in ~60% of pts with familial disease and 10% of subjects with sporadic disease.
Diastolic dysfunction without left ventricular hypertrophy is an early finding in children with HCM-causing mutations in the beta-myosin heavy chain, alpha-tropomyosin, and myosin-binding protein C genes Poutanen T, et al. (12)	To compare biomarkers, LVH and diastolic function in children with a HCM mutation (genotype positive) versus healthy control children	Cohort study from a single center	53 children	27 children with a HCM mutation and 28 controls (mutation negative).	Clinical analyses of 27 children with HCM mutations (genotype +) compared to age-matched children without mutations.	Genotype-positive children had thicker septal measurements compared to the control children (p=.004), but only 3 (11%) genotype-positive children fulfilled criteria for body surface area adjusted maximal LV thickness of healthy children. However all genotype-positive children had prolonged isovolumetric relaxation time, increased left atrial volume, or increased levels of NT-proANP.	This study confirms LVH is a late manifestation of HCM. Children with HCM mutations have other clinical abnormalities including diastolic dysfunction.
Myofilament protein gene mutation screening and outcome of pts with HCM Olivotto I, et al. (13)	Assessment of clinical course in pts with a known mutation versus pts in whom no mutation is defined.	Cohort study from a single center	203 HCM pts	87 pts with a mutation and 126 pts without a mutation. 8 myofilament genes were sequenced (MYH7, MYBPC3, TNNT2, TPM1, TNNI3, MYL3, MYL2, ACTC) and clinical course assessed over a mean of 4 y.	Cardiovascular death, nonfatal stroke, or progression to NYHA class III or IV.	Despite similar baseline features, pts with HCM mutations had increased risk of the combined endpoints of cardiovascular death, nonfatal stroke, or progression to NYHA class III or IV compared with the pts without mutations. Mutation positive pts also had greater LV dysfunction (systolic and diastolic abnormalities) in comparison to mutation negative pts	This study showed a direct relationship between a positive genotype and outcomes in HCM. Unlike pts in whom no mutation was identified, those with a sarcomere gene mutation had a significantly poorer prognosis.

Compound and double mutations in pts with HCM: implications for genetic testing and counseling Ingles J, et al. (14)	To compare the clinical phenotypes in carries of one or multiple HCM mutations.	Cohort genetic and clinical study	80 unrelated HCM index pts and family members	19 index pts with 1 mutation, 4 index pts and 11 family members with >1 mutation.	Clinical manifestations and course (SD, transplant, etc) in single and multiple mutation subjects.	5% of the HCM cohort had >1 mutation. 6 of 14 (43%) of affected individuals with >1 HCM mutation had sudden cardiac death vs. 10 of 55 (18%) in affected individuals with 1 mutation. There was an increased LVH in pts with >1 mutations (mean: 30.7 mm) vs. 24.4 mm in pts with 1 mutation.	Multiple gene mutations cause more severe HCM possible due to a “double dose” effect.

DNA indicates deoxyribonucleic acid; EKG, electrocardiogram; HCM, hypertrophic cardiomyopathy; LV, left ventricular; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NYHA, New York Heart Association; patients; pts; and SD, sudden death.

Data Supplement 2. Invasive Therapies Table

Study Name/Author (Citation)	Aim of Study	Study Design	Study Size	Patient Population	Endpoints	Results	Comments
Usefulness of clinical, echocardiographic, and procedural characteristics to predict outcome after percutaneous transluminal septal myocardial ablation. van der Lee C, et al. (15)	To assess outcomes after septal ablation	Multiple center retrospective review of consecutive pts	131 pts	HCM pts treated with septal ablation	Complications (in-hospital; follow-up); unsuccessful therapy	Ablation success in 90%; complications in 15% including death in 3.8%.	Long-term success was related to procedural volume.
Septal myotomy-myectomy and transcoronary septal alcohol ablation in hypertrophic obstructive cardiomyopathy. A comparison of clinical, haemodynamic and exercise outcomes. Firoozi S, et al. (16)	To compare subjective outcomes among HCM pts undergoing surgical myectomy and septal ablation	Single center retrospective review	44 pts	24 HCM pts treated with surgical myectomy; 20 HCM pts treated with septal ablation	Echocardiographic gradient; NYHA class; cardiopulmonary exercise testing;	Gradient and NYHA improvements were similar between the 2 treatment modalities. Objective exercise parameters improved more with surgical myectomy.	
Long-term effects of surgical septal myectomy on survival in pts with obstructive HCM. Ommen SR, et al. (17)	To determine impact of surgical myectomy on long-term survival	Multiple center retrospective review of concurrent patient cohorts	1337 pts	289 HCM pts treated with surgical myectomy; 228 pts with obstructive HCM treated pharmacologically; 820 nonobstructive HCM pts	Overall and cardiac survival	1, 5, and 10 y survival (98%, 96%, and 83%, respectively) after surgical myectomy is equivalent to healthy age and gender matched population. Overall and cardiac survival superior to that of obstructive pts not offered operation.	30-d mortality = 0.8%. Annualized cardiac mortality rate 0.5% per/y
Hypertrophic obstructive cardiomyopathy: comparison of outcomes after myectomy or alcohol ablation adjusted by propensity score. Ralph-Edwards A, et al. (18)	Review of early outcomes after surgical myectomy or septal ablation	Single center retrospective review of concurrent patient cohorts	150 pts	90 HCM pts treated with surgical myectomy; 60 HCM pts treated with septal ablation	Survival, NYHA class, echocardiographic gradient	Superior 4 y survival, gradient reduction, and NYHA class improvement were observed in the myectomy pts after adjusting for baseline differences.	

Current effectiveness and risks of isolated septal myectomy for hypertrophic obstructive cardiomyopathy. Smedira NG, et al. (19)	To assess effectiveness and risks of surgical myectomy	Single center retrospective review of consecutive pts	323 pts	HCM pts treated with surgical myectomy	Echocardiographic gradient; NYHA class; need for reintervention for HCM	Gradient decreased from 68 mmHg to 17 mmHg ; no in-hospital mortality; freedom from reintervention at 8 y was 92%;	
Outcome of alcohol septal ablation for obstructive HCM. Sorajja P, et al. (20)	Assess outcomes after septal ablation	Single center retrospective review	138 pts	HCM pts treated with septal ablation	Gradient, survival, complications	Relief of LVOT gradient 83% (p<0.001); 1.4% procedural death rate with ablation; 4 y overall survival = 88%; 4 y survival free from NYHA class III to IV symptoms was 76% after ablation.	Posthoc Analysis: among pts age <65 y, survival free of symptoms was better with myectomy.
Clinical and echocardiographic determinants of long-term survival after surgical myectomy in obstructive HCM. Woo A, et al. (21)	Determine clinical and echocardiographic factors associated with long-term morbidity and mortality after surgical myectomy	Single center retrospective review of consecutive pts	338 pts	HCM pts treated with surgical myectomy	Mortality, predictors of mortality, NYHA class	Early post-op mortality = 1.5%, 10 y survival = 83+/-3%; Improvement to NYHA class I to II observed in 83%	Predictors of major CV events were age, female sex, preoperative AF, concomitant CABG and preoperative left atrial size
Follow-up of alcohol septal ablation for symptomatic hypertrophic obstructive cardiomyopathy. The Baylor and Medical University of South Carolina experience, 1996 to 2007. Fernandes VL, et al. (22)	Determine long-term outcome after alcohol septal ablation	Retrospective review of consecutive pts	629 pts	HCM pts treated with alcohol septal ablation	Mortality, complications, repeat invasive therapy for HCM pacemaker requirement, and NYHA class	Early mortality = 1%, 1, 5, 8 y survival (97%, 92%, 89%, respectively), Permanent pacemaker required in 8.2%. Mean NYHA class at 4-5 y decreased from 2.8 +/- 0.6 to 1.2 +/-0.5 (p<0.001) = 1.2	
Transcatheter ablation of septal hypertrophy for hypertrophic obstructive cardiomyopathy: feasibility, clinical benefit, and short term results in elderly pts. Gietzen FH, et al. (23)	Evaluate symptomatic and hemodynamic results of septal ablation in elderly pts	Single center retrospective review of consecutive pts	157 pts	HCM pts treated with septal ablation. Group I age <60 y, Group II age ≥60 y.	Mortality, gradient, complications, NYHA class	Early mortality similar between groups. Total mortality 3.8% in Group I vs. 9.1% in Group II. Similar improvement in symptoms and exercise time. Pts age ≥60 y more likely to have persistent atrioventricular heart block (5% vs. 17%, p=0.015. NYHA class improved from 2.7 to 1.4 in Group I and 3.0 to 1.7 in Group II.	

Survival after transcatheter ablation of septal hypertrophy in hypertrophic obstructive cardiomyopathy (TASH): a 10 year experience. Kuhn H, et al. (24)	Determine impact of septal ablation on survival	Single center retrospective review of consecutive pts	644 pts	HCM pts treated with septal ablation	Mortality (early and late)	Early mortality = 1.2%, annual mortality = 3.2% per/ y	Early and late mortality improved after converting to low alcohol dosing
Long-Term Outcomes in High-Risk Symptomatic Pts With HCM Undergoing Alcohol Septal Ablation. Kwon DH, et al. (25)	Assess outcomes after septal ablation in high-risk pts	Single center retrospective review	55 pts	HCM pts at high risk for cardiac surgery treated with septal ablation	Gradient, quality of life, NYHA class, mortality	Gradient and quality of life improved at 3 mo and sustained through 1 y. Reduction in number of pts with NYHA class ≥ 3 (93% NYHA class >2). Early mortality = 2%, 1, 5, 10 y survival (96%, 87%, 76%)	
Comparison of ethanol septal reduction therapy with surgical myectomy for the treatment of hypertrophic obstructive cardiomyopathy. Nagueh SF, et al. (26)	Compare hemodynamic efficacy of surgical myectomy and septal ablation	Multicenter retrospective case-control comparison	82 pts	41 HCM pts treated with septal ablation; 41 age and gradient matched HCM pts treated with surgical myectomy	Gradient, NYHA class, exercise capacity	At 1 y after procedure, improvements in gradient, symptoms and exercise capacity were similar between the 2 groups	
Outcome of pts with hypertrophic obstructive cardiomyopathy after percutaneous transluminal septal myocardial ablation and septal myectomy surgery. Qin JX, et al. (27)	Evaluate results of surgical myectomy as compared to septal ablation	Single center retrospective review	51 pts	25 HCM pts treated with septal ablation; 26 HCM pts treated with surgical myectomy	Gradient, NYHA class	Gradient reduction more robust with surgery; NYHA improvements similar	Ablation pts in this study were on average 15 y older than myectomy pts
Updated meta-analysis of septal alcohol ablation versus myectomy for HCM. Agarwal S, et al. (28)	Compare outcomes of HCM pts undergoing surgical myectomy with septal ablation	Meta-analysis	12 published studies	HCM pts treated with either surgical myectomy or septal ablation	Mortality, complications, NYHA class, gradient	No differences in mortality, NYHA class, ventricular arrhythmia, or need for reintervention. Ablation pts had higher residual gradient and rate of advanced conduction abnormalities.	

Meta-analysis of septal reduction therapies for obstructive HCM. Comparative roles of overall mortality and SCD after treatment. Leonardi RA, et al. (29)	Compare outcomes of HCM pts undergoing surgical myectomy with septal ablation	Meta-analysis	27 published studies	HCM pts treated with either surgical myectomy or septal ablation	Survival and rate of SCD	No differences were observed between the treatment strategies in terms of overall, cardiac or sudden death related survival	

CABG indicates coronary artery bypass graft; CV, cardiovascular; HCM, hypertrophic cardiomyopathy; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; patients; pts; and SCD, sudden cardiac death.

Data Supplement 3. Pacing Table

Study Name/Author (Citation)	Aim of Study	Study Design	Study Size	Patient Population	Endpoints	Results	Comments
Functional assessment of pts treated with permanent dual-chamber pacing as a primary treatment for HCM McDonald, K, et al. (30)	To determine the improvement in objective exercise capacity in pts with HCM undergoing DDD pacing	Cohort 2 center trial - DDD pacemaker implanted in all pts	11 pts (mean age 50 +/- 12 y)	Eleven selected pts with obstructive HCM and severe symptoms refractory to drug therapy studied at 2 centers who underwent initial implantation of a DDD pacemakers.	Symptoms, NYHA class and exercise time	Within 1 wk, there was an improvement in NYHA class in all pts. The exercise duration increased from 7.7 to 11.5 min. In 5 pts at a follow-up of 3 mo to 1y, there was an increase in exercise time from 6.2 to 8.8 min.	One of the first studies which showed an improvement in exercise time during continuous DDD pacing.
Effects of dual-chamber pacing in HCM Jeanrenaud, X, et al. (31)	To determine the effects of acute and long-term dual-chamber pacing in pts with HCM.	Cohort series. Acute pacing study and long-term implantation of a dual-chamber pacemaker.	13 pts with acute study and 8 pts with follow-up (age 56 +- 14 y)	Selected pts with obstructive HCM and severe symptoms refractory to drug therapy	NYHA class, outflow tract gradient.	At a follow-up of 14 +/- 11 mo, NYHA class had decreased from III to II in terms of dyspnea. Outflow tract gradient had decreased from 67 +/- 42 to 17 +/- 10 mmHg. When the pacemaker was turned off at follow-up, the gradient was 31 +/- 36 mmHg.	This study showed that synchronized and ventricular pacing in at an optimal atrioventricular interval does reduce intraventricular pressure gradient at the time of acute study. There is a long-term drop in pressure gradient during chronic pacing with improvement in functional tolerance.
Long-term results of dual chamber pacing in obstructive HCM: evidence for progressive symptomatic and hemodynamic improvement and reduction of LVH Fananapazir, L, et al. (32)	To determine the intermediate term outcome of DDD pacing in pts with HCM.	Cohort single center trial - implant DDD pacemakers in all pts	84 pts (mean age 49 +/-16 y)	Consecutive pts with obstructive HCM and severe symptoms refractory to drug therapy referred to a single center	Symptoms, NYHA class, LVOT gradient, LVH	At a mean follow-up of 2.3 +/- 0.8 y, there was improvement in NYHA class (3.2 +/- 0.5 to 1.6 +/- 0.6, p<.0001). The LVOT gradient decreased from 100 +/- 47 mmHg to 29 +/- 34 mmHg - p<.01. A subset of pts had reversal of LV wall thickness.	The high success rate of DDD pacing in this cohort trial has not been replicated in subsequent randomized pacing trials.

DDD pacing in HCM: A multicentre clinical experience Slade, A, et al. (33)	To determine the outcome of DDD pacing in pts with HCM.	Cohort multicentre trial. Implant DDD pacemaker in all pts.	56 pts from 4 centers,(mean age 48 +/- 18 y)	Selected pts with obstructive HCM and severe symptoms refractory to drug therapy	Symptoms, NYHA class, LVOT gradient	44 out of 53 pts had an improvement in functional class. At a mean follow-up of 11 +/- 11 mo, there was a reduction in gradient from 78 +/- 31 to 36 +/- 25 mmHg.	There was symptomatic improvement in the majority of pts. However, there was no correlation between the magnitude of the gradient drop and the functional improvement. This is another study that showed the results of acute temporary pacing studies had no correlation with outcome. Thus, there remains a discrepancy between perceived symptomatic benefit and modest objective improvement. Also, optimal outcome was achieved only with continued pharmacologic treatment.
Pacing in hypertrophic obstructive cardiomyopathy: A randomized crossover study Kappenberger, L, et al. (34)	To determine the intermediate term outcome of DDD pacing in pts with HCM.	Randomized multicenter single blind crossover study. Pts then randomized to 12 wks of activated pacing or inactivated pacing in a single blind crossover study.	83 pts (mean age 53 :25-87 y)	Pts with obstructive HCM and severe symptoms refractory to drug therapy. The pts all had acute hemodynamic response to pacing.	Symptoms, exercise duration, and gradient	NYHA class improved from 2.4 to 1.4 for dyspnea and 1.0 to 0.4 for angina (p<0.007). Quality of life showed improvement. After 12 wks of pacing, the gradient fell from 59 +/- 36 to 30 +/- 25 mmHg with active pacing. Exercise tolerance improved by 21%, but only in those pts who at baseline had a severe limitation of <10 min at Bruce protocol.	This trial showed clinical and hemodynamic benefit for pts with hypertrophic obstructive cardiomyopathy and LVOT obstruction. This multicenter trial included only pts who had an acute hemodynamic response >30% reduction in gradient in the catheterization laboratory. There was no overall change in exercise time when looking at all pts. Although 70% improved, the degree of improvement was not related to acute hemodynamic results.

Dual-chamber pacing for HCM: A randomized, double-blind, crossover trial Nishimura, R, et al. (35)	To determine the intermediate term outcome of DDD pacing in pts with HCM	Randomized double-blind crossover study. Pts randomized for 3 mo each of DDD pacing and back-up AAI pacing.	21 pts (Mean age 58; 35-74 y).	Single center trial of selected pts with obstructive HCM and severe symptoms refractory to drug therapy	Symptoms, NYHA class, LVOT gradient, quality of life, treadmill time, peak VO ₂ .	6 mo of follow-up, LVOT gradient had decreased from 76 +/- 61 to 55 +/- 38 mmHg after DDD pacing and 83 +/- 59 mmHg after AAI pacing. Quality of life and exercise duration were significantly improved from the baseline state compared to the DDR, but not significantly different between the DDD arm and the back-up arm. 63% of pts had symptomatic improvement during the DDD arm, but 42% had symptomatic improvement during the AAI arm. Peak oxygen consumption did not differ significantly. Symptoms did not change in 31% and 5% experienced deterioration of symptoms.	This trial showed that dual-chamber pacing may relieve symptoms and decrease gradient in pts with HCM, but there are some pts in whose symptoms do not change and become even worse. Symptomatic improvement may occur without hemodynamic benefit suggesting the role of a placebo effect.
Significant improvement of quality of life following atrioventricular synchronous pacing in pts with hypertrophic obstructive cardiomyopathy. Data from 1 year of follow-up Gadler, F, et al. (36)	To determine the outcome of pacing on quality of life during 1 y follow-up.	Cohort trial - implant DDD pacemaker in all pts	83 pts (mean age 53, 32-87 y).	Pts with obstructive HCM and severe symptoms refractory to drug therapy.	NYHA class and Karolinska quality of life.	At the end of 1 y, no patient had hemodynamic deterioration. NYHA class I (36 pts follow-up vs. 0 pts initial); NYHA class II (31 pts follow-up vs. 37 pts initial); NYHA class III (8 pts follow-up vs./ 45 pts initial). 76 of the pts preferred pacing and 4 pts preferred AAI mode.	This study showed that atrioventricular synchronous pacing had a beneficial effect on most domains of quality of life at 1 y follow-up.

Assessment of permanent dual-chamber pacing as a treatment for drug-refractory symptomatic pts with obstructive HCM. A randomized, double-blind, crossover study (M-PATHY) Maron, B, et al. (37)	To determine the intermediate term outcome of DDD pacing in pts with HCM.	Randomized double-blind crossover study. DDD pacing implants in all pts, randomized then to a DDD mode and pacing back-up AAI mode in a double-blind crossover study design, followed by an uncontrolled 6-mo pacing trial.	48 pts (age 53 +/- 17, 22-83 y).	Pts with obstructive HCM and severe symptoms refractory to drug therapy	Symptoms, NYHA class, LVOT gradient, quality of life, treadmill time, peak VO₂.	DDD versus AAI mode comparison at 6 mo indicated no significant change in exercise capacity, quality of life, or NYHA class. During a 12-mo follow-up of 6 further mo of continuous pacing, there was a significant increase in functional class and quality of life, but no change in peak oxygen consumption. The gradient was reduced from 82 +/- 32 mmHg to 48 +/- 32 mmHg. There was no change in gradient in 43%. Only 12% had a clinical response (improvement in NYHA class, quality of life, treadmill time), and these were all pts age >65 y.	This trial showed perceived symptomatic improvement was most consistent with a substantial placebo effect during the randomization process. Longer uncontrolled pacing periods had subjective benefit, but did not have objective improvement in cardiovascular performance and there was only modest reduction in outflow tract gradient.
Dual chamber pacing for pts with hypertrophic obstructive cardiomyopathy: A clinical perspective in 2000. Erwin, J, et al. (38)	To determine the long-term outcome of pts with HCM.	Cohort trial (single center) DDD pacemakers implanted in all pts	28 pts (56 +/- 16 y)	Pts with obstructive HCM and severe symptoms refractory to drug therapy	Symptoms and LVOT gradient.	At a follow-up of 24 +/- 14 mo (max 50 mo), 47% of pts improved but 53% of pts did not improve in terms of symptomatic response. LVOT gradient decreased from 95 +/- 40 to 62 +/- 47 mmHg.	This is a much lower "success" rate with long-term follow-up of pts who underwent dual-chamber pacing, with less than half of the pts having symptomatic improvement. There was no difference in the gradient response between those pts who improved versus those who did not improve. The residual gradient was still >60 mmHg, which is severe obstruction.
Long-term follow-up of pts with obstructive HCM treated with dual-chamber pacing. Megevand, A, et al. (39)	To determine the long-term outcome of DDD pacing in pts with HCM.	Single center cohort trial. DDD pacemaker implanted in all pts.	18 pts (mean age 47 y)	Pts with obstructive HCM and severe symptoms refractory to drug therapy. Only pts who had an initial acute hemodynamic benefit	Outflow tract gradient and NYHA class	At the end of a follow-up of 49 +/- 33 mo, the gradient of 82 +/- 35 dropped to 32 +/- 23. There was a beneficial result in NYHA class from 2.4 to 1.8.	This study reports the long-term outcome of a cohort of pts who had a dual-chamber pacemaker implanted who had a beneficial acute hemodynamic study. There was a significant reduction in symptoms as well as sustained decrease in LVOT obstruction at a follow-up of over 4 years.

HCM indicates hypertrophic cardiomyopathy; LV, left ventricular; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; NYHA, New York Hear Association; VO₂, oxygen consumption and patients, pts.

Data Supplement 4. Sudden Cardiac Death Risk Factor Table

Study Name/Author (Citation)	Aim Of Study	Study Design	Study Size	Patient Population	End-points	Results								Comments
						FHSCD	MLVWT	NSVT	SYNCOPE	ABPR	LVOTO	Multiple RF		
Prospective prognostic assessment of blood pressure response during exercise in pts with HCM. Sadoul N, et al. (40)	Assess prognostic significance of blood pressure response to exercise in HCM pts	Single center prospective data collection of consecutive pts	161 pts	HCM pts age ≤40 y	SD	Univariate					OR: 3.0, p<0.005			
						Multi-variate								
SD in HCM: Identification of high-risk pts. Elliott PM, et al. (41)	Identify HCM pts at high risk for SCD	Single center prospective data collection of consecutive pts	368 pts	HCM pts. Exclusions: prior SCD event, current amiodarone use, incomplete risk assessment age <40 y	SD	Univariate	p=0.15	OR: 4.1, p=0.001	p=0.21	p=0.13	OR: 2.4, p=0.04		2 or more RF: OR: 5.6, p=0.0001	
						Multivariate	Combined with syncope (OR: 5.3, p=0.002)	OR: 2.9, p=0.03	p=0.18	Combined with family history (OR: 5.3, p=0.002)	p=0.22			
Prognostic significance of 24 hour ambulatory electrocardiographic monitoring in pts with HCM: a prospective study. Maron BJ, et al. (42)	Assess prognostic significance of 24 h ambulatory ECG monitoring in HCM pts	Single center prospective data collection of consecutive pts	84 pts	HCM pts. Exclusions: myectomy pts	SD	Univariate			p=0.02					
						Multi-variate								

Prognosis of asymptomatic pts with HCM and NSVT. Spirito P, et al. (43)	Assess prognostic significance of NSVT in asymptomatic or mildly symptomatic HCM pts	3 center retrospective study	151 pts	HCM Pts. Exclusions: prior syncope, NYHA class >2; any cardioactive medications	SD	Univariate			p=0.24					
						Multi-variate								
Prognostic value of NSVT and the potential role of amiodarone treatment in HCM assessment in an unselected non-referral based patient population. Cecchi F, et al. (44)	Evaluate antiarrhythmic therapy in HCM pts	Single center registry	167 pts	HCM Pts. Exclusions: amiodarone use and/or absence of 24 h ambulatory ECG	Cardiac and SD	Univariate			NS					Only 1 SD in entire study population
						Multi-variate								
Predictors of SCD in HCM. Maki S, et al. (44)	Identify HCM pts at high risk for SCD	Single center data collection.	309 pts	HCM pts, consecutive	SD	Univariate	p=0.03	p=0.33	p=0.41	p=0.07	p=0.0002	p=0.0009		
						Multi-variate								
Magnitude of LVH and risk of SD in HCM Spirito P, et al.	Assess the relation between LVH and survival in	2 centers retrospective data collection	480 pts	HCM Pts; excluded pts with prior cardiac arrest and/or	SD	Univariate	p=0.23					p=0.0006		

(45)	HCM pts			no follow up		Multi-variate		OR: 1.76 per 5 mm increase, p=0.003				p=0.76		
Relation between severity of LVH and prognosis in pts with HCM. Elliott PM, et al. (46)	Assess prognostic significance of LVH in relation to other SCD risk factors	Single center data collection.	630 pts	HCM pts, consecutive	SD or ICD discharge	Univariate		OR: 1.31 per 5 mm increase, p=0.03					OR: 2.1, p=0.0001	
						Multi-variate		OR: 1.26 per 5 mm increase, p=0.06					OR: 2.0, p=0.0001	
Maximum left ventricular thickness and risk of SD in pts with HCM. Olivotto I, et al. (47)	Assess relationship between LVH and outcome in HCM pts	Single center data collection.	237 pts	HCM pts, consecutive	SD or ICD discharge	Univariate		p=0.27						
						Multi-variate								
LVOT and SD risk in pts with HCM. Elliott PM, et al. (48)	Assess influence of symptoms and LVOTO on risk for SCD in HCM pts	Single center data collection.	917 pts	HCM pts, consecutive	SD or ICD discharge	Univariate							OR: 1.8-2.0, p<0.001	
						Multi-variate	OR: 1.9, p=0.04	p=0.2	OR: 3.8, p<0.0001	OR: 2.3, p=0.01	p=0.3	OR: 1.01 per mmHg, p=0.002		OR: 3.8 if LVOTO >90 mmHg, p=0.005
Syncope and risk of SD in HCM. Spirito P, et al. (49)	Assess clinical implications of syncope in	Multicenter data collection	1511 pts	HCM pts, consecutive	SD or ICD discharge	Univariate				p=0.08				

	HCM pts					Multi-variate	p=0.12	p=0.06		p=0.29;		p=0.29		For unexplained syncope <6 mo prior to evaluation, OR: 4.9, p=0.006

ABPR indicates abnormal blood pressure response; ECG, electrocardiogram; FHSCD, family history of sudden cardiac death; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LVH, left ventricular hypertrophy; LVOTO, left ventricular outflow tract obstruction; MLVWT, maximum left ventricular wall thickness; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; OR, odds ratio; patients; pts; RF, risk factor; SCD, sudden cardiac death and SD, sudden death.

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Non-surgical reduction of the myocardial septum

1 Guidance

- 1.1 Current evidence on the safety and efficacy of non-surgical reduction of the myocardial septum appears adequate to support the use of the procedure, provided that normal arrangements are in place for consent, audit and clinical governance.
- 1.2 The procedure should only be performed in specialist units by clinicians who have had adequate training in the technique. The British Cardiovascular Intervention Society has agreed to produce standards for training.

2 The procedure

2.1 Indications

- 2.1.1 Non-surgical reduction of the myocardial septum is used to treat outflow tract obstruction in patients with hypertrophic obstructive cardiomyopathy (HOCM). Patients with HOCM have abnormally thickened heart muscle, which narrows the outflow tract from the left ventricle, often causing chest pain, breathlessness, palpitations and fainting spells. There is an increased risk of sudden death from heart attacks or abnormal heart rhythms.
- 2.1.2 Most patients with HOCM are treated with medication. More invasive treatments may be considered in patients who still get symptoms despite drug treatment. The standard surgical treatment is ventricular septal myotomy-myectomy, using an open surgical technique that requires cardiopulmonary bypass.

2.2 Outline of the procedure

- 2.2.1 Non-surgical reduction of the myocardial septum does not require open chest surgery or cardiopulmonary bypass. It involves inserting a catheter into the femoral artery and passing it up into the heart under X-ray control. Alcohol is injected into an artery that supplies blood to the septum. This destroys a part of the muscle in the septum, which then becomes thinner.

2.3 Efficacy

- 2.3.1 The studies showed that non-surgical reduction of the myocardial septum is efficacious in the short term. In three non-randomised studies, the mean reduction in gradient across the left ventricular outflow tract (LVOT) ranged from 22 mmHg to 42 mmHg, and compared favourably to the mean reduction in LVOT gradient for open surgery. The studies also reported reduced numbers of patients suffering from severe breathlessness and fainting spells after treatment. There is, however, a lack of long-term follow-up. For more details, refer to the Sources of evidence (see below).
- 2.3.2 The Specialist Advisors considered the procedure to be an established alternative to surgical relief of outflow tract obstruction in patients with HOCM.

Interventional Procedure Guidance 40

This guidance is written in the following context:

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

Interventional procedures guidance is for health professionals and people using the NHS in England, Wales and Scotland.

2.4 Safety

- 2.4.1 In the studies, the most commonly reported complication was the need for patients to have a pacemaker implanted permanently because of complete heart block following the procedure. In one non-randomised study of 41 patients, 9 patients (22%) required a permanent pacemaker. The same study reported one procedure-related death. For more details, refer to the Sources of evidence (see below).
- 2.4.2 The Specialist Advisors cited a 10% risk of complete heart block, requiring patients to have a permanent pacemaker implanted after having the procedure. The Advisors considered the procedure to be safe when performed by experienced operators in specialist units with an established interest in HOCM.

2.5 Other comments

- 2.5.1 Skilled use of ultrasound is required to identify the blood supply to the hypertrophic myocardium, and thus control the infarct size.
- 2.5.2 Appropriate patient selection is essential.

Andrew Dillon
Chief Executive
February 2004

Information for the Public

NICE has produced information describing its guidance on this procedure for patients, carers and those with a wider interest in healthcare. It explains the nature of the procedure and the decision made, and has been written with patient consent in mind. This information is available, in English and Welsh, from www.nice.org.uk/IPG40publicinfo.

Sources of evidence

The evidence considered by the Interventional Procedures Advisory Committee is described in the following document.

Interventional procedure overview of non-surgical reduction of myocardial septum, November 2002

Available from: www.nice.org.uk/IP018overview

Ordering information

Copies of this guidance can be obtained from the NHS Response Line by telephoning 0870 1555 455 and quoting reference number N0435. *Information for the Public* can be obtained by quoting reference number N0436 for the English version and N0437 for a version in English and Welsh.

The distribution list for this guidance is available on the NICE website at URL www.nice.org.uk/IPG040distributionlist

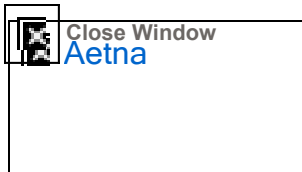
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National Institute for Clinical Excellence

MidCity Place, 71 High Holborn, London WC1V 6NA, website: www.nice.org.uk

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Clinical Policy Bulletin:
Percutaneous Transluminal Septal Myocardial Ablation (PTSMA)
Number: 0558

Policy

1. Aetna considers percutaneous transluminal septal myocardial ablation (PTSMA) by alcohol-induced septal branch occlusion medically necessary for hypertrophic obstructive cardiomyopathy (HOCM) in adults when all of the following criteria are met:
 1. Member has severe symptoms (e.g., dyspnea, angina pectoris, [pre]syncope, palpitations or heart failure) for at least 6 months despite optimal drug therapy (e.g., beta-blockers, calcium-antagonists), dual chamber pacing therapy and/or ineffective previous surgical myotomy/myectomy; *and*
 2. Member is classified as New York Heart Association class III or IV (see below); *and*
 3. Member has a classical, asymmetric subaortic HOCM identified by echocardiography, and not a mid-ventricular, a concealed membranous subaortic stenosis, nor supravalvular form; *and*
 4. Echocardiography shows left ventricular wall thickness of greater than 13 mm in adults in the absence of another cause for left ventricular hypertrophy; 15 mm in an athlete; *and*
 5. Member has systolic anterior motion of the mitral valve on echocardiography; *and*
 6. Member has a resting left ventricular outflow tract (LVOT) gradient of greater than 30 mm Hg or a stressed gradient of greater than 60 mm Hg, or member has less severe

Policy History

▮ [Last Review](#): 09/07/2012
Effective: 08/14/2001
Next Review: 07/11/2013

▮ [Review History](#)
▮ [Definitions](#)

Additional Information

▮ [Clinical Policy Bulletin Notes](#)

- symptoms and LVOT of greater than 50 mm Hg at rest or greater than 100 mm Hg under stress; *and*
7. Member does not have coronary artery disease that would preclude performance of the procedure.
 2. Aetna considers percutaneous transluminal septal myocardial ablation experimental and investigational for all other indications because of insufficient evidence of its safety and effectiveness.

Background

Hypertrophic obstructive cardiomyopathy (HOCM), also known as idiopathic hypertrophic subaortic stenosis, is a primary, sometimes familial and genetically determined myocardial hypertrophy with an incidence of about 0.2 %. About 25 % of the patients have dynamic left ventricular outflow tract (LVOT) obstruction, which usually develops during puberty and increases in severity until the age of 18 to 20 years. Not infrequently, HOCM is diagnosed for the first time in the elderly.

Echocardiography is the primary method for diagnosing HOCM. This condition is characterized by a super-normally contracting left ventricle, asymmetric septal hypertrophy, which affects mainly the interventricular septum, increased ventricular wall thickness (left ventricular wall thickness of greater than 13 mm in adults in the absence of another cause for left ventricular hypertrophy; 15 mm in an athlete), and systolic anterior motion of the mitral valve. Although patients with hypertrophic cardiomyopathy usually have super-normal ejection fractions, they have thickened and poorly compliant left ventricles in which left ventricular filling pressure is markedly elevated and probably is responsible for most of the symptoms.

Cardiac hypertrophy is associated with LVOT obstruction in only a minority of HOCM patients. The LVOT gradient is generated by systolic anterior motion of a mitral valve leaflet and its coaptation with the interventricular septum. Left ventricular outflow tract obstruction does not generally increase during exercise because of adequate venous return, but it often worsens or becomes apparent in the immediate post-exercise period. Maneuvers that decrease preload or afterload or increase myocardial contractility, such as stress, dehydration, and sudden adoption of an erect posture often induce symptoms. The significance of the LVOT gradient has been debated, but it is now generally accepted that it is an important determinant of the clinical course.

Asymptomatic adult patients probably do not require therapy or risk stratification studies, unless there is a malignant family history of sudden death or occupational need (airline pilot). Management decisions are dominated by the need to address sometimes disabling symptoms of dyspnea, angina pectoris, stress-induced syncope,

palpitations or heart failure, and risk of sudden death. Treatment of symptomatic patients with HOCM aims at reduction of the LVOT gradient and improvement of diastolic filling either by pharmacological therapy with negative inotropic drugs (beta-blockers, calcium-antagonists), permanent DDD pacemaker therapy (i.e., dual-chamber, dual-pacing, dual-sensing), or surgical myotomy/myectomy.

At least 10 % of patients with severe HCOM are unresponsive to medical therapy or report severe side effects of optimum doses of drugs. Successful DDD pacing at the apex of the right ventricle induces a paradoxical motion of the inter-ventricular septum away from the mitral valve, reducing LVOT obstruction. Long-term studies have uniformly confirmed that DDD pacing can reduce LVOT gradient and improve severe drug-refractory symptoms in most patients with HOCM, obviating the need for cardiac surgery. A large European study has demonstrated that when follow-up was sufficiently long to allow adaptive changes and to eliminate carryover effects, DDD pacing conferred substantial symptomatic and hemodynamic benefits. As some of the beneficial effects of DDD pacing become apparent after prolonged pacing, it is important to allow sufficient time for chronic DDD pacemaker therapy.

Left ventricular myotomy and myectomy (Morrow's procedure) has been the standard therapy for patients with severe symptoms (New York Heart Association (NYHA) functional class III to IV) that persist despite adequate pharmacotherapy and DDD pacing. Using an aortic root approach, this involves surgically removing enough muscle from the septum to sufficiently widen the outflow tract. The procedure improves or eliminates symptoms and LVOT gradient in 90 % of patients. The success of the procedure and the operative mortality are very much dependent on the skill and experience of the surgeon but may be as low as 1 to 2 %. Complications include heart block, ventricular septal defect, 1 to 2 % annual mortality during follow-up, late aortic valve incompetence, and LV dysfunction. Sometimes, a prosthetic mitral valve replacement must be done to eliminate systolic anterior motion and LVOT obstruction, but the patient requires life-long anti-coagulation and is subject to the risk of prosthetic malfunction.

In 1994, as an alternative to surgery, non-surgical percutaneous transluminal septal myocardial ablation (PTSMA) by alcohol-induced septal branch occlusion was introduced to decrease LVOT gradient and improve symptoms in patients with HOCM. This method was substantially improved by the introduction of echocardiographic guidance in 1996. With this guidance, the reduction in the LVOT gradient is optimized and ablation of inappropriate areas can be avoided. Consequently, the hemodynamic results and symptoms are improved, and the incidence of complications is reduced. The most common procedural complication is the development of high-grade trifascicular block necessitating implantation of a permanent pacemaker

in 25 % of patients. Other complications include death, ventricular arrhythmias, and coronary artery dissection.

Percutaneous transluminal septal myocardial ablation involves transcatheter selection of 1 or 2 small septal branches of the left anterior descending artery, threading a small, short, low-pressure angioplasty balloon into position to occlude the artery, and the instillation of absolute alcohol into the myocardium. The resultant localized myocardial infarction reduces the amount of septal myocardium, opening up the LVOT. Compared with surgical myectomy, the literature shows that PTSMA has the advantage of being minimally invasive, easily repeated, and with relatively low major morbidity/mortality risk for patients with co-morbid conditions.

In one study, 70 % of patients during short-term follow-up showed impressive clinical improvement as well as diminution of intra-ventricular pressure gradient and a marked increase in maximal workload during exercise testing. During a 12-month follow-up period, there was a significant decrease of functional class, a reduced rate of syncope, and a reduced degree of mitral insufficiency. Exercise capacity, oxygen uptake and the cardiac index increased, intra-ventricular gradient, the end diastolic pressure of the left ventricle and the left atrial size decreased. Additionally, there was a decrease in the septal thickness with increase in the cross-sectional area of the outflow tract. PET examination showed an ablation-induced local myocardial defect. There was also evidence for improved diastolic function. Electrophysiological and Holter monitor studies indicated no increased arrhythmogenicity. The in-hospital mortality rate amounts to about 1.8 % and in 15 % of patients a second PTSMA is necessary.

There appears to be little doubt in the literature that favorable morphologic and functional results can be achieved by PTSMA, and that short-term follow-up studies show clinical and objective improvement, as well as further gradient reduction due to left ventricular remodeling. Currently, randomized, prospective studies of larger patient series are being conducted to compare the short- and long-term effects of PTSMA with the major treatment options (e.g., pharmacologic therapy, myotomy/myectomy, mitral valve replacement, pacemaker implantation). The outcomes of these studies will be needed to determine PTSMA's ultimate role in the treatment of HOCM, as well as provide guidance concerning the optimal treatment of patients with HOCM.

The American Heart Association and the American College of Cardiology have no position statements on this procedure.

An assessment by the National Institute of Clinical Excellence (NICE, 2003) concluded that current evidence on the safety and efficacy of non-surgical reduction of the myocardial septum appears adequate to support

the use of the procedure, provided that normal arrangements are in place for consent, audit and clinical governance.

Percutaneous transluminal septal myocardial ablation is best performed in centers with experience with this procedure. Patients treated with PTSMA should be entered into a registry of these procedures.

Zhang and colleagues (2011) retrospectively summarized the effect of non-medical therapies for pediatric patients with HOCM. From November 2008 to June 2010, 4 children with drug-refractory HOCM were admitted to the authors' hospital. Their ages were 14, 7, 9 and 6 years old, respectively. Their body weights were 38, 17, 21.5 and 17 kg, respectively. Before operation, the LVOT gradients were 60, 147, 58 and 114 mm Hg (1 mm Hg = 0.133 kPa), respectively; mitral regurgitation (MR) areas were 2.2, 7.3 cm² and 2.9 cm², respectively, except that it was trivial in 1 case. Percutaneous transluminal septal myocardial ablation was performed in case 1 and 2. Septal myectomy (SM) was performed in case 3 and 4. Follow-up was first performed right after operation or before discharge, then 1 month, 3 months, 6 months, and 12 months after operation, and then once-yearly. The follow-up period was 1 to 18 (9.3 +/- 8.1) months. All patients experienced relieved symptoms; 3 of them had their NYHA functional class improved except case 2. Echocardiography revealed that LVOT gradients right after operations were 38, 79, 20 and 0 mm Hg, respectively, suggesting significant improvement of LVOT obstruction in all patients. During follow-up, case 2 suffered from recurrence of LVOT obstruction, while the other 3 cases showed sustained relief. In the last follow-up, the LVOT gradients of the 4 patients were 19, 168, 16 and 0 mm Hg, respectively. Echocardiography also revealed that MRs of all patients were significantly reduced, even in case 2 whose LVOT gradient rebounded, with no recurrence during follow-up. Severe complications were absent, such as ventricular septum perforation, cardiac tamponade, ventricular tachycardia or ventricular fibrillation. No one suffered from complete heart block. Transient complete right bundle branch block (CRBBB) was observed in case 1 after PTSMA and converted to intra-ventricular block after 1 month. Complete left bundle branch block (CLBBB) was present in both case 3 and 4, who received SM. In case 4, it converted to intra-ventricular block after 1 month while in case 3 CLBBB persisted. The authors concluded that the initial experience showed that PTSMA and SM were safe and effective for drug-refractory symptomatic HOCM children, with satisfactory short-term results. They stated that further studies are needed to evaluate the long-term results and complications.

Appendix

The New York Heart Association (NYHA) classification is as follows:

Class I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

CPT Codes / HCPCS Codes / ICD-9 Codes

There is no specific CPT code for percutaneous transluminal septal myocardial ablation:

Other HCPCS codes related to the CPB:

C1886 Catheter, extravascular tissue ablation, any modality (insertable)

ICD-9 codes covered if selection criteria are met:

425.1 Hypertrophic obstructive cardiomyopathy [see criteria]

Other ICD-9 codes related to the CPB:

413.0 - 413.9 Angina pectoris

414.00 - Coronary atherosclerosis [CAD could preclude
414.07 performance of procedure]

428.0 - 428.9 Heart failure

780.2 Syncope and collapse [presyncope]

785.1 Palpitations

786.09 Other dyspnea and respiratory abnormalities

V45.01 Cardiac pacemaker in situ

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Medical Policy

Subject: Alcohol Septal Ablation for Treatment of Hypertrophic Cardiomyopathy

Policy #: SURG.00133

Current Effective Date: 10/09/2012

Status: New

Last Review Date: 08/09/2012

Description/Scope

Alcohol septal ablation for treatment of hypertrophic cardiomyopathy (HCM) was developed as a less invasive alternative to open surgical septal resection in adults. This document addresses alcohol septal ablation for the treatment of HCM. HCM has also been referred to in the published literature as hypertrophic obstructive cardiomyopathy (HOCM).

Position Statement

Medically Necessary:

Alcohol septal ablation is considered **medically necessary** as a treatment of hypertrophic cardiomyopathy (HCM) in adults (age 21 and older) when all of the following criteria are met:

- Severe heart failure symptoms (New York Heart Association [NYHA] class III or IV) or other exertional symptoms (such as syncope or near syncope) refractory to drug therapy; **and**
- Left ventricular outflow tract (LVOT) gradient greater than or equal to 50 mm Hg at rest or with physiological provocation, including but not limited to: exercise, valsalva maneuver or amyl nitrate.

Investigational and Not Medically Necessary:

Alcohol septal ablation is considered **investigational and not medically necessary** when all of the above criteria are not met.

Rationale

Clinical evidence evaluating alcohol septal ablation indicates that in adults, the procedure may result in improvement of various signs and symptoms including NYHA classification, exercise time, LVOT gradient, and septal thickness as measured by echocardiography. There is a lack of randomized trials evaluating the procedure; however, case series, meta-analyses and practice guidelines are available.

In an early case series, Seggewiss and colleagues (1999) reported on 114 individuals with symptomatic HCM who underwent treatment with alcohol septal ablation. LVOT gradient was reduced in 94% of subjects from a mean of 73.8 mm Hg to 18.6 mm Hg with the gradient further declining at the 3-month follow-up. The NYHA classification also improved. A total of 11 (9.6%) individuals required a permanent pacemaker due to trifascicular block and 2 individuals (1.8%) died during the hospital stay. Kuhn and colleagues (2000) reported on a case series of 215 alcohol septal ablation procedures in 187 individuals. The perioperative mortality rate was 2.3%. At a mean follow-up of 2.4 years, the NYHA classification had decreased from 3.0 to 1.6. Similar to the data reported by Seggewiss, there were significant improvements in cardiodynamic measures, including

outflow gradient and septal thickness. Gietzen and colleagues (1999) reported on 62 individuals with HCM undergoing alcohol septal ablation, all of whom had substantial clinical improvement. The procedure-related early mortality was 4%, and a permanent pacemaker was required in 40% of the cases. Lakkis and colleagues (2000) reported on the 1-year follow-up of 50 individuals with HCM undergoing alcohol septal ablation. A total of 16% required permanent pacemaker implantation. There were 2 perioperative deaths (4%). Prior to the procedure, all reported either NYHA Class III or IV symptoms compared to none at 1-year follow-up. Improvement in cardiodynamic assessments was consistent with the clinical improvements.

More recent studies confirm earlier reported results in individuals with HCM. Fernandes and colleagues (2008) evaluated long-term outcomes of alcohol septal ablation. Six hundred and twenty-nine subjects were enrolled consecutively from 1996 to 2007. A total of 98.4% (n = 619) underwent alcohol septal ablation with 92% follow-up in 2007. During the procedure, ethanol (2.6 +/- 1.0 ml) was injected into 1.3 +/- 0.5 septal arteries, inducing a septal infarct. Complications included death 1% (n = 6), permanent pacemaker requirement 8.2% (n = 52), coronary dissection 1.3% (n = 8), and worsening mitral regurgitation 0.3% (n = 2). The mean follow-up was 4.6 +/- 2.5 years (range: 3 months to 10.2 years). During follow-up, NYHA functional class decreased from 2.8 +/- 0.6 to 1.2 +/- 0.5 (p < 0.001); Canadian Cardiovascular Society angina score decreased from 2.1 +/- 0.9 to 1.0 +/- 0 (p < 0.001); and exercise time increased from 4.8 +/- 3.3 to 8.2 +/- 1.0 (p < 0.001) min. The resting and provoked LVOT gradients decreased progressively (p < 0.001) and remained low during follow-up. The septal thickness decreased from 2.1 +/- 0.5 cm to 1.0 +/- 0.1 cm (p < 0.001) and the ejection fraction decreased from 68 +/- 9% to 62 +/- 3% (p < 0.001). The survival estimates at 1, 5, and 8 years were 97%, 92%, and 89%, respectively. The initial benefits of alcohol septal ablation were maintained during follow-up.

Nageuh and colleagues (2011) reported predictors of clinical outcomes of alcohol septal ablation for the treatment of HOCM. A total of 874 individuals who underwent alcohol septal ablation were enrolled in a multicenter North American Registry. A majority of the subjects (64%) had severe obstruction at rest, and the remaining had provocable obstruction. Prior to ablation, it was noted that 78% of the subjects had severe dyspnea (NYHA functional class III or IV) and 43% had severe angina (Canadian Cardiovascular Society angina class III or IV) with or without dyspnea. Significant improvement occurred after ablation; however, there were 81 deaths (9.3%). Survival estimates at 1, 5, and 9 years were 97%, 86%, and 74%, respectively. Survival appeared better after alcohol septal ablation as compared to those who did not undergo septal reduction therapy. Variables which predicted mortality after ablation, included baseline ejection fraction and NYHA functional class, the number of septal arteries injected with ethanol, post-ablation septal thickness, beta-blocker use, and the number of ablation procedures.

Multiple meta-analyses are also available in the published literature comparing outcomes of alcohol septal ablation with septal myectomy for treatment of HCM (Agarwal, 2009; Alam, 2009; Leonardi, 2010). Similar mortality rates and functional status were observed for both treatments in the meta-analyses, however; limitations of alcohol septal ablation reported included conduction abnormalities and a higher post-intervention LVOT gradient.

Gersh and colleagues (2011) of the American College of Cardiology Foundation/American Heart Association Task Force on Practice guidelines issued a guideline for the diagnosis and treatment of HCM which includes the following invasive therapy recommendations:

Class I

1. Septal reduction therapy should be performed only by experienced operators in the context of a comprehensive HCM clinical program and only for the treatment

of eligible patients with severe drug-refractory symptoms and LVOT obstruction.† (Level of Evidence: C)

*Experienced operators are defined as an individual operator with a cumulative case volume of at least 20 procedures or an individual operator who is working in a dedicated HCM program with a cumulative total of at least 50 procedures.

†Eligible patients are defined by all of the following:

- a. Clinical: Severe dyspnea or chest pain (usually NYHA functional classes III or IV) or occasionally other exertional symptoms (such as syncope or near syncope) that interfere with everyday activity or quality of life despite optimal medical therapy.
- b. Hemodynamic: Dynamic LVOT gradient at rest or with physiologic provocation 50 mm Hg associated with septal hypertrophy and SAM of the mitral valve.
- c. Anatomic: Targeted anterior septal thickness sufficient to perform the procedure safely and effectively in the judgment of the individual operator.

CLASS IIa

1. Consultation with centers experienced in performing both surgical septal myectomy and alcohol septal ablation is reasonable when discussing treatment options for eligible patients with HCM with severe drug-refractory symptoms and LVOT obstruction. (Level of Evidence: C)
2. Surgical septal myectomy, when performed in experienced centers, can be beneficial and is the first consideration for the majority of eligible patients with HCM with severe drug-refractory symptoms and LVOT obstruction. (Level of Evidence: B)
3. Surgical septal myectomy, when performed at experienced centers, can be beneficial in symptomatic children with HCM and severe resting obstruction (>50 mm Hg) for whom standard medical therapy has failed. (Level of Evidence: C)
4. When surgery is contraindicated or the risk is considered unacceptable because of serious comorbidities or advanced age, alcohol septal ablation, when performed in experienced centers, can be beneficial in eligible adult patients with HCM with LVOT obstruction and severe drug-refractory symptoms (usually NYHA functional classes III or IV). (Level of Evidence: B)

CLASS IIb

1. Alcohol septal ablation, when performed in experienced centers, may be considered as an alternative to surgical myectomy for eligible adult patients with HCM with severe drug-refractory symptoms and LVOT obstruction when, after a balanced and thorough discussion, the patient expresses a preference for septal ablation. (Level of Evidence: B)
2. The effectiveness of alcohol septal ablation is uncertain in patients with HCM with marked (i.e., >30 mm) septal hypertrophy, and therefore the procedure is generally discouraged in such patients. (Level of Evidence: C)

CLASS III: HARM

1. Septal reduction therapy should not be done for adult patients with HCM who are asymptomatic with normal exercise tolerance or whose symptoms are controlled or minimized on optimal medical therapy. (Level of Evidence: C)
2. Septal reduction therapy should not be done unless performed as part of a program dedicated to the longitudinal and multidisciplinary care of patients with HCM. (Level of Evidence: C)
3. Mitral valve replacement for relief of LVOT obstruction should not be performed in patients with HCM in whom septal reduction therapy is an option. (Level of Evidence: C)
4. Alcohol septal ablation should not be done in patients with HCM with concomitant disease that independently warrants surgical correction (e.g., coronary artery bypass grafting for CAD, mitral valve repair for ruptured chordae) in whom surgical myectomy can be performed as part of the operation. (Level of Evidence: C)
5. Alcohol septal ablation should not be done in patients with HCM who are less than 21 years of age and is discouraged in adults less than 40 years of age if myectomy is a viable option. (Level of evidence: C)

Levels of Evidence and Classification of Recommendations:

Levels of evidence:

Level A: Multiple populations evaluated. Data derived from multiple randomized clinical trials or meta-analyses.

Level B: Limited populations evaluated. Data derived from a single randomized trial or nonrandomized studies.

Level C: Very limited populations evaluated. Only consensus opinion of experts, case studies, or standard of care.

Classification of Recommendations:

CLASS I: Procedure/Treatment **SHOULD** be performed/administered.

CLASS IIa: Additional studies with focused objectives needed. IT IS **REASONABLE** to perform procedure/administer treatment.

CLASS IIb: Additional studies with broad objectives needed; additional registry data would be helpful. Procedure/Treatment **MAY BE CONSIDERED**.

CLASS III: No benefit or may cause harm.

In summary, the data suggests that alcohol septal ablation for the treatment of HCM is associated with symptomatic and cardiodynamic improvement in adults under specific circumstances. Risks associated with the procedure include that of complete heart block requiring implantation of a permanent pacemaker, as well as an increased risk of sustained ventricular arrhythmias. Alcohol septal ablation is not recommended for children due to a lack of published evidence supporting its use in this age group.

Background/Overview

HCM is a complex cardiac disease associated with diverse clinical, morphologic and pathophysiologic manifestations. One of the most characteristic abnormalities is a hypertrophied and nondilated left ventricle, which may impair diastolic filling. When the hypertrophy results in left ventricular outflow obstruction, the development of dyspnea, angina, syncope, or congestive heart failure may occur. Pharmacologic therapies include beta blockers or calcium-channel blockers to decrease the heart rate with a consequent prolongation in diastole and increased passive ventricular filling. If medical therapy is insufficient to control symptoms, strategies to reduce the

outflow obstruction may be considered. Surgical reaction focuses on removing a small amount of myocardium at the base of the septum (myotomy-myomectomy).

Alcohol septal ablation for treatment of HCM has been considered as an alternative to open surgical septal resection in adults. The technique involves infusion of ethanol through an angioplasty catheter threaded into the septal perforator branches of the left anterior descending artery to infarct and subsequently thin the bulging septum. A key component of the procedure is the identification of the target vessels. A balloon catheter is introduced into the septal branches. The balloon is inflated and contrast injected into the balloon lumen to delineate the area supplied by the septal branch and to ensure that the balloon inflation would prevent spillage of the subsequent injection of alcohol into the left anterior descending artery.

Definitions

Canadian Cardiovascular Society Score: This organization defines anginal classes as follows:

- Class I - Ordinary physical activity does not cause angina;
- Class II - Slight limitation of ordinary activity;
- Class III - Marked limitation of ordinary physical activity;
- Class IV - Inability to carry on physical activity without discomfort.

Left ventricular outflow tract (LVOT) gradient: A measurement often used to evaluate the severity of HCM, the presence or absence of LVOT obstruction, and the efficacy of treatment.

New York Heart Association (NYHA) functional class: A four-tier system that categorizes based on subjective impression of the degree of functional compromise. The four NYHA functional classes are as follows:

- Class I - Individuals with cardiac disease but without resulting limitation of physical activity; ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain; symptoms only occur on severe exertion;
- Class II - Individuals with cardiac disease resulting in slight limitation of physical activity; they are comfortable at rest; ordinary physical activity, (e.g., moderate physical exertion, such as carrying shopping bags up several flights of stairs) results in fatigue, palpitation, dyspnea, or anginal pain;
- Class III - Individuals with cardiac disease resulting in marked limitation of physical activity; they are comfortable at rest; less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain;
- Class IV - Individuals with cardiac disease resulting in inability to carry on any physical activity without discomfort; symptoms of heart failure or the anginal syndrome may be present even at rest; if any physical activity is undertaken, discomfort is increased.

Septal myectomy: A surgical procedure performed to reduce the muscle thickening that occurs in individuals with HCM.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. A draft of future ICD-10 Coding (effective 10/01/2014) related to this document, as it might look today, is included below for your reference. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider

reimbursement policy Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

CPT

93799 Unlisted cardiovascular service or procedure [when specified as alcohol septal ablation]

ICD-9 Diagnosis

425.11-425.18 Hypertrophic cardiomyopathy

ICD-10 Procedure *ICD-10-PCS draft codes; effective 10/01/2014:*

025M3ZZ Destruction of ventricular septum, percutaneous approach

ICD-10 Diagnosis *ICD-10-CM draft codes; effective 10/01/2014:*

I42.1-I42.2 Hypertrophic cardiomyopathy

When services are Investigational and Not Medically Necessary:

For the procedure and diagnosis codes listed above when criteria are not met.

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Alcohol Septal Ablation (ASA)
 Ethanol Septal Ablation
 Non-surgical Septal Reduction
 Percutaneous Transluminal Septal Ablation in Hypertrophic Obstructive Cardiomyopathy
 Septal Reduction Therapy
 Sigwart Procedure
 Transcoronary Ablation of Septal Hypertrophy (TASH)

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

Document History

Status	Date	Action
New	08/09/2012	Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development.

Oscillating devices for airway clearance in people with cystic fibrosis (Review)

Morrison L, Agnew J



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[Intervention Review]

Oscillating devices for airway clearance in people with cystic fibrosis

Lisa Morrison¹, Jennifer Agnew²

¹West of Scotland Adult CF Unit, Gartnavel General Hospital, Glasgow, UK. ²Chest and Cystic Fibrosis Clinic, The Hospital for Sick Children, Toronto, Canada

Contact address: Lisa Morrison, West of Scotland Adult CF Unit, Gartnavel General Hospital, 1053 Great Western Road, Glasgow, G12 0YN, UK. Januarykids@aol.com. Lisa.Morrison@ggc.scot.nhs.uk.

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ABSTRACT

Background

Chest physiotherapy is widely prescribed to assist the clearance of airway secretions in people with cystic fibrosis (CF). Oscillating devices generate intra- or extra-thoracic oscillations orally or external to the chest wall. Internally they create variable resistances within the airways, generating controlled oscillating positive pressure which mobilises mucus. Extra-thoracic oscillations are generated by forces outside the respiratory system, e.g. high frequency chest wall oscillation.

Objectives

To determine the effectiveness and acceptability of oscillating devices compared to other forms of physiotherapy to improve respiratory function, mucus clearance and other outcomes in people with CF.

Search strategy

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register comprising references identified from comprehensive electronic database searches and hand searches of relevant journals and abstract books of conference proceedings.

Latest search of the CF Trials Register: 3rd December 2010.

Selection criteria

Randomised controlled studies and controlled clinical studies of oscillating devices compared with any other form of physiotherapy in people with CF.

Data collection and analysis

Two authors independently applied the inclusion criteria to publications and assessed the quality of the included studies.

REVIEW

High-frequency chest compression: A summary of the literature

Cara F Dosman MD FRCPC FAAP¹, Richard L Jones PhD FCCP²

CF Dosman, RL Jones. High-frequency chest compression: A summary of the literature. *Can Respir J* 2005;12(1):37-41.

The purpose of the present literature summary is to describe high-frequency chest compression (HFCC), summarize its history and outline study results on its effect on mucolysis, mucus transport, pulmonary function and quality of life. HFCC is a mechanical method of self-administered chest physiotherapy, which induces rapid air movement in and out of the lungs. This mean oscillated volume is an effective method of mucolysis and mucus clearance. HFCC can increase independence. Some studies have shown that HFCC leads to more mucus clearance and better lung function compared with conventional chest physiotherapy. However, HFCC also decreases end-expiratory lung volume, which can lead to increased airway resistance and a decreased oscillated volume. Adding positive end-expiratory pressure to HFCC has been shown to prevent this decrease in end-expiratory lung volume and to increase the oscillated volume. It is possible that the HFCC-induced decrease in end-expiratory lung volume may result in more mucus clearance in airways that remain open by reducing airway size. Adjunctive methods, such as positive end-expiratory pressure, may not always be needed to make HFCC more effective.

Key Words: Chest physiotherapy; End-expiratory lung volume; High-frequency chest compression; Mucus clearance; Positive end-expiratory pressure

Patients with cystic fibrosis have excessively thick lung mucus, which tends to plug the small peripheral airways. The cycle of hypersecretion, infection (1), inflammation and impaired mucus clearance (2,3) leads to progressive airway obstruction and destruction, especially in the lung periphery where cough and conventional chest physiotherapy are less effective at clearing mucus (3,4).

High-frequency chest compression (HFCC) is a patient-delivered form of chest physiotherapy, which causes mucolysis (5,6), as well as increased mucus clearance (7-10) and improvement in pulmonary function (1,10,11) compared with that achieved by conventional chest percussion and postural drainage. Also called high-frequency oscillation, HFCC was initially administered only to patients with cystic fibrosis, but is now starting to be used for a wide range of pulmonary, neurological and neuromuscular disorders (12).

DESCRIPTION AND HISTORY OF HFCC

HFCC is a portable mechanical method of self-administered chest physiotherapy (13), and is analogous to frequent repetitive coughing (7). Cough generates a shear stress at the air-mucus

Vibrations mécaniques de haute fréquence : Sommaire de la littérature

Le but du présente résumé de la littérature est de décrire la technique de vibrations mécaniques de haute fréquence, d'en résumer l'histoire et de donner un aperçu des résultats d'une étude ayant mesuré ses effets sur la mucolyse, le dégagement du mucus, la fonction pulmonaire et la qualité de vie. Les vibrations mécaniques de haute fréquence sont une technique de physiothérapie pulmonaire auto-administrée qui accélèrent l'entrée et la sortie de l'air durant la respiration. Cette technique stimule efficacement la mucolyse et l'élimination du mucus et peut de ce fait favoriser l'autonomie. Certaines études ont montré qu'elle favorise l'expectoration et améliore la fonction pulmonaire comparativement à la physiothérapie pulmonaire classique. Par contre, elle réduit également le volume pulmonaire télé-expiratoire et peut entraîner une résistance respiratoire accrue et une baisse du volume oscillatoire. L'ajout d'une pression télé-expiratoire s'est révélée susceptible d'atténuer la baisse du volume pulmonaire télé-expiratoire et d'accroître le volume oscillatoire. Il est possible que la diminution du volume télé-expiratoire induite par les vibrations mécaniques de haute pression favorise une plus grande élimination du mucus dans les voies aériennes qui restent ainsi dégagées, en réduisant le calibre des voies respiratoires. Des méthodes d'appoint, comme la pression positive télé-expiratoire ne seraient pas toujours nécessaires pour rendre cette technique plus efficace.

interface (14), which increases mucus flow rate (15). Repetitive cough induces significantly more mucus clearance than a single cough, and even more clearance with an increased frequency of repetitive cough or air flow oscillations (14,16). Therefore, it follows that rapid air movement may also enhance mucus clearance.

HFCC is delivered by a pneumatic vest that surrounds the thorax. The vest is inflated to a nearly constant (11) positive background pressure with a superimposed frequency of air pressure oscillations (17). These oscillations induce rapid air movement in and out of the lungs, which is measured at the mouth as mean oscillated volume. Mean oscillated volume increases mucus clearance (11), particularly from the periphery of the lung (18). The volume of mucus moved has been thought to be greatest at frequencies between 10 Hz and 20 Hz, which can be alternated to maximize the volume of air and rate of air flow (19). HFCC may be advantageous in patients with cystic fibrosis in which plugging of the peripheral airways is a major problem and in patients with other obstructive lung disease where peripheral mucociliary clearance is impaired and cough is less effective (18).

Departments of ¹Pediatrics and ²Medicine, University of Alberta, Edmonton, Alberta

Correspondence and reprints: Dr Cara F Dosman, Glenrose Rehabilitation Hospital, 10230-111 Avenue, Edmonton, Alberta T5G 0B7.

Telephone 780-471-8235, fax 780-471-7907, e-mail caradosman@cha.ab.ca

British Thoracic Society guideline for respiratory management of children with neuromuscular weakness

Jeremy Hull,¹ Roona Aniapravan,² Elaine Chan,³ Michelle Chatwin,⁴ Julian Forton,⁵ Jayne Gallagher,¹ Neil Gibson,⁶ Jill Gordon,⁷ Imelda Hughes,³ Renee McCulloch,⁸ Robert Ross Russell,² Anita Simonds⁴

► Additional appendices are published online only. To view these files please visit the journal online (<http://thorax.bmj.com/content/67/S1.toc>).

¹Department of Paediatrics, Oxford University Hospitals NHS Trust, Oxford, UK

²Department of Paediatrics, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

³Royal Manchester Children's Hospital, Manchester, UK

⁴National Institute of Health Research Respiratory Biomedical Research Unit, Royal Brompton and Harefield NHS Foundation Trust, UK

⁵University Hospital of Wales, Cardiff, UK

⁶Royal Hospital for Sick Children, Glasgow, UK

⁷Child Development Centre, Suffolk Community Healthcare, UK

⁸Great Ormond St Hospital, London, UK

Correspondence to

Jeremy Hull, Level 2, Children's Hospital, John Radcliffe Hospital, Oxford, OX3 9DU, UK; jeremy.hull@ouh.nhs.uk

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SUMMARY OF RECOMMENDATIONS

Identifying children at risk of respiratory complications

- Clinical assessment of respiratory health should be part of every medical consultation for children with neuromuscular weakness (NMW) and should be directed towards identifying progressive muscle weakness, ability to cope with respiratory infection, aspiration, progression of scoliosis and sleep-disordered breathing. [D]
- Ulna length or armspan should be used to predict lung function in children with neuromuscular disease whose height cannot be accurately measured. [B]
- Vital capacity should be measured in all patients with neuromuscular disease who are capable of performing spirometry as part of the respiratory assessment. [C]
- Cough peak flow should be used as part of the assessment of effective secretion clearance in children with neuromuscular disease over the age of 12 years.
- Assessment for sleep-disordered breathing should be carried out no less than annually for children with neuromuscular disease who have a vital capacity of <60% predicted and for children who have become non-ambulant because of progressive muscle weakness or who never attain the ability to walk. [D]
- Assessment for sleep-disordered breathing should be carried out no less than annually for all infants with weakness, children with NMW who have symptoms of obstructive sleep apnoea or hypoventilation, children with clinically apparent diaphragmatic weakness and children with rigid spine syndromes. [√]
- In young children whose rate of disease progression is uncertain, or in older children who have shown a clinical deterioration or who are suffering with repeated infections, or who develop symptoms of sleep-disordered breathing, sleep assessment may need to be more frequent than once a year. [√]
- All children with abnormal overnight oximetry should undergo more detailed sleep monitoring with at least oxycapnography. [√]
- When there is doubt about the cause of sleep-disordered breathing, overnight polysomnography or sleep polygraphy should be performed. [√]
- Portable overnight oxycapnography or polygraphy in the home may be the most appropriate option for some patients. [√]

- Children with neuromuscular disease with a history of swallowing difficulties should have a feeding assessment by a speech and language therapist including a video fluoroscopy swallow assessment if the swallow is thought to be unsafe. [√]

Airway clearance and respiratory muscle training

- Children with ineffective cough (including children over 12 years of age with cough peak flow <270 litres/min), particularly if they have had episodes of deterioration with respiratory infection, should be taught augmented cough techniques. [C]
- Manual cough assist and air-stacking methods to achieve maximum insufflation capacity are effective methods of improving cough efficiency and should be used when appropriate. [C]
- Mechanical insufflation/exsufflation (MI-E) should be considered in very weak children, those with loss of bulbar function, and those who cannot cooperate with manual cough assist or air-stacking or in whom these methods are not effective. [C]
- Oscillatory techniques such as high-frequency chest wall oscillation and intrapulmonary percussive ventilation should be considered in children who have difficulty mobilising secretions or who have persistent atelectasis, despite use of other airway clearance techniques. [D]
- Airway clearance techniques should be used during respiratory infection when oxygen saturation levels fall below 95% while the child is breathing room air. If the techniques being used fail to result in an increase in oxygen saturation to 95% or above, different methods of airway clearance should be used. This may require attendance at hospital for treatment. [D]
- MI-E should be available in the acute setting in all hospitals that treat neuromuscular patients as an alternative method of airway clearance with the purpose of preventing deterioration and the need for intubation and mechanical ventilation. [D]
- Nebulised normal saline may be considered in children who have continued tenacious secretions. [√]
- Humidification should be considered in children who use non-invasive ventilation (NIV) and who have tenacious airway secretions. Care should be taken to ensure that use of humidification does not result in a troublesome increase in oral secretions. [√]
- When using sputum mobilising techniques, appropriate emergency equipment (eg, resuscitation bag

Local Coverage Determination (LCD) for High Frequency Chest Wall Oscillation Devices (L12739)

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Jump to Section...	▼
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Contractor Information

Contractor Name Noridian Back to Top	Contract Number 19003	Contract Type DME MAC

LCD Information

Document Information

LCD Database ID Number L12739	Jurisdiction Alaska American Samoa Arizona California - Entire State Northern Mariana Islands Guam Hawaii Iowa Idaho Kansas Missouri - Entire State Montana North Dakota Nebraska Nevada Oregon South Dakota Utah Washington Wyoming
LCD Title High Frequency Chest Wall Oscillation Devices	
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Original Effective Date
For services performed on or after 10/01/2003

Revision Effective Date
For services performed on or after 05/01/2013

Revision Ending Date
N/A

Retirement Date
N/A

Notice Period Start Date
06/01/2003

Notice Period End Date
N/A

CMS National Coverage Policy

Coverage Guidance

Coverage Indications, Limitations and/or Medical Necessity

For any item to be covered by Medicare, it must 1) be eligible for a defined Medicare benefit category, 2) be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member, and 3) meet all other applicable Medicare statutory and regulatory requirements. For the items addressed in this local coverage determination, the criteria for "reasonable and necessary", based on Social Security Act § 1862(a)(1)(A) provisions, are defined by the following indications and limitations of coverage and/or medical necessity.

For an item to be covered by Medicare a detailed written order (DWO) must be received by the supplier before a claim is submitted. If the supplier bills for an item addressed in this policy without first receiving the completed DWO, the item will be denied as not reasonable and necessary.

High frequency chest wall oscillation devices (HFCWO) (E0483) are covered for beneficiaries who meet:

A. Criterion 1, 2, or 3, and

B. Criterion 4

1. There is a diagnosis of cystic fibrosis (ICD-9 277.00, 277.02).
2. There is a diagnosis of bronchiectasis (ICD-9 011.50-011.56, 494.0, 494.1, 748.61) which has been confirmed by a high resolution, spiral, or standard CT scan and which is characterized by:
 - a. Daily productive cough for at least 6 continuous months; or

- b. Frequent (i.e., more than 2/year) exacerbations requiring antibiotic therapy.

Chronic bronchitis and chronic obstructive pulmonary disease (COPD) in the absence of a confirmed diagnosis of bronchiectasis do not meet this criterion.

3. The beneficiary has one of the following neuromuscular disease diagnoses:
 - Post-polio (138)
 - Acid maltase deficiency (277.6)
 - Anterior horn cell diseases (335.0-335.9)
 - Multiple sclerosis (340)
 - Quadriplegia (344.00-344.09)
 - Hereditary muscular dystrophy (359.0, 359.1)
 - Myotonic disorders (359.21-359.29)
 - Other myopathies (359.4, 359.5, 359.6, 359.89)
 - Paralysis of the diaphragm (519.4)
4. There must be well-documented failure of standard treatments to adequately mobilize retained secretions.

If all of the criteria are not met, the claim will be denied as not reasonable and necessary.

It is not reasonable and necessary for a beneficiary to use both an HFCWO device and a mechanical in-exsufflation device (E0482).

Replacement supplies, A7025 and A7026, used with beneficiary owned equipment, are covered if the beneficiary meets the criteria listed above for the base device, E0483. If these criteria are not met claims will be denied as not reasonable and necessary.

REFILL REQUIREMENTS

For Durable Medical Equipment, Prosthetics, Orthotics, and Supplies (DMEPOS) provided on a recurring basis, billing must be based on prospective, not retrospective use. For DMEPOS products that are supplied as refills to the original order, suppliers must contact the beneficiary prior to dispensing the refill and not automatically ship on a pre-determined basis, even if authorized by the beneficiary. This shall be done to ensure that the refilled item remains reasonable and necessary, existing supplies are approaching exhaustion, and to confirm any changes or modifications to the order. Contact with the beneficiary or designee regarding refills must take place no sooner than 14 calendar days prior to the delivery/shipping date. For delivery of refills, the supplier must deliver the DMEPOS product no sooner than 10 calendar days prior to the end of usage for the current product. This is regardless of which delivery method is utilized. (CMS Program Integrity Manual, Internet-Only Manual, CMS Pub. 100-8, Chapter 5, Section 5.2.6).

For all DMEPOS items that are provided on a recurring basis, suppliers are required to have contact with the beneficiary or caregiver/designee prior to dispensing a new supply of items. Suppliers must not deliver refills without a refill request from a beneficiary. Items delivered without a valid, documented refill request will be denied as not reasonable and necessary.

Suppliers must not dispense a quantity of supplies exceeding a beneficiary's expected utilization.

Suppliers must stay attuned to changed or atypical utilization patterns on the part of their clients. Suppliers must verify with the ordering physicians that any changed or atypical utilization is warranted.

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Coding Information

Bill Type Codes:

Contractors may specify Bill Types to help providers identify those Bill Types typically used to report this service. Absence of a Bill Type does not guarantee that the policy does not apply to that Bill Type. Complete absence of all Bill Types indicates that coverage is not influenced by Bill Type and the policy should be assumed to apply equally to all claims.

Revenue Codes:

Contractors may specify Revenue Codes to help providers identify those Revenue Codes typically used to report this service. In most instances Revenue Codes are purely advisory; unless specified in the policy services reported under other Revenue Codes are equally subject to this coverage determination. Complete absence of all Revenue Codes indicates that coverage is not influenced by Revenue Code and the policy should be assumed to apply equally to all Revenue Codes.

CPT/HCPCS Codes

Group 1 Paragraph: The appearance of a code in this section does not necessarily indicate coverage.

HCPCS MODIFIERS:

EY - No physician or other licensed health care provider order for this item or service

GA - Waiver of liability statement issued as required by payer policy, individual case

GZ - Item or service expected to be denied as not reasonable and necessary

KX – Requirements specified in the medical policy have been met

HCPCS CODES:

Group 1 Codes:

A7025 HIGH FREQUENCY CHEST WALL OSCILLATION SYSTEM VEST, REPLACEMENT
FOR USE WITH PATIENT OWNED EQUIPMENT, EACH

A7026 HIGH FREQUENCY CHEST WALL OSCILLATION SYSTEM HOSE, REPLACEMENT
FOR USE WITH PATIENT OWNED EQUIPMENT, EACH

E0483 HIGH FREQUENCY CHEST WALL OSCILLATION AIR-PULSE GENERATOR
SYSTEM, (INCLUDES HOSES AND VEST), EACH

ICD-9 Codes that Support Medical Necessity

Group 1 Paragraph: The presence of an ICD-9 code listed in this section is not sufficient by itself to assure coverage. Refer to the section on "Indications and Limitations of Coverage and/or Medical Necessity" for other coverage criteria and payment information.

Group 1 Codes:

	TUBERCULOUS BRONCHIECTASIS UNSPECIFIED EXAMINATION -
011.50 -	TUBERCULOUS BRONCHIECTASIS TUBERCLE BACILLI NOT FOUND BY
011.56	BACTERIOLOGICAL OR HISTOLOGICAL EXAMINATION BUT TUBERCULOSIS
	CONFIRMED BY OTHER METHODS (INOCULATION OF ANIMALS)
138	LATE EFFECTS OF ACUTE POLIOMYELITIS
277.00	CYSTIC FIBROSIS WITHOUT MECONIUM ILEUS
277.02	CYSTIC FIBROSIS WITH PULMONARY MANIFESTATIONS
277.6	OTHER DEFICIENCIES OF CIRCULATING ENZYMES
335.0 -	WERDNIG-HOFFMANN DISEASE - ANTERIOR HORN CELL DISEASE
335.9	UNSPECIFIED
340	MULTIPLE SCLEROSIS
344.00 -	QUADRIPLÉGIA UNSPECIFIED - OTHER QUADRIPLÉGIA
344.09	
359.0	CONGENITAL HEREDITARY MUSCULAR DYSTROPHY
359.1	HEREDITARY PROGRESSIVE MUSCULAR DYSTROPHY
359.21 -	MYOTONIC MUSCULAR DYSTROPHY - OTHER SPECIFIED MYOTONIC
359.29	DISORDER
359.4 -	TOXIC MYOPATHY - SYMPTOMATIC INFLAMMATORY MYOPATHY IN
359.6	DISEASES CLASSIFIED ELSEWHERE
359.89	OTHER MYOPATHIES
494.0	BRONCHIECTASIS WITHOUT ACUTE EXACERBATION
494.1	BRONCHIECTASIS WITH ACUTE EXACERBATION
519.4	DISORDERS OF DIAPHRAGM
748.61	CONGENITAL BRONCHIECTASIS

Group 1 Asterisk: N/A

ICD-9 Codes that DO NOT Support Medical Necessity
All ICD-9 codes that are not specified in the previous section.

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General Information

Associated Information

DOCUMENTATION REQUIREMENTS

Section 1833(e) of the Social Security Act precludes payment to any provider of services unless "there has been furnished such information as may be necessary in order to determine the amounts due such provider." It is expected that the beneficiary's medical records will reflect the need for the care provided. The beneficiary's medical records include the physician's office records, hospital

records, nursing home records, home health agency records, records from other healthcare professionals and test reports. This documentation must be available upon request.

PRESCRIPTION (ORDER) REQUIREMENTS

GENERAL (PIM 5.2.1)

All items billed to Medicare require a prescription. An order for each item billed must be signed and dated by the treating physician, kept on file by the supplier, and made available upon request. Items dispensed and/or billed that do not meet these prescription requirements and those below must be submitted with an EY modifier added to each affected HCPCS code.

DISPENSING ORDERS (PIM 5.2.2)

Equipment and supplies may be delivered upon receipt of a dispensing order except for those items that require a written order prior to delivery. A dispensing order may be verbal or written. The supplier must keep a record of the dispensing order on file. It must contain:

- Description of the item
- Beneficiary's name
- Prescribing Physician's name
- Date of the order and the start date, if the start date is different from the date of the order
- Physician signature (if a written order) or supplier signature (if verbal order)

For the “Date of the order” described above, use the date the supplier is contacted by the physician (for verbal orders) or the date entered by the physician (for written dispensing orders).

Signature and date stamps are not allowed. Signatures must comply with the CMS signature requirements outlined in PIM 3.3.2.4.

The dispensing order must be available upon request.

For items that are provided based on a dispensing order, the supplier must obtain a detailed written order before submitting a claim.

DETAILED WRITTEN ORDERS (PIM 5.2.3)

A detailed written order (DWO) is required before billing. Someone other than the ordering physician may produce the DWO. However, the ordering physician must review the content and sign and date the document. It must contain:

- Beneficiary's name
- Physician's name

- Date of the order and the start date, if start date is different from the date of the order
- Detailed description of the item(s) (see below for specific requirements for selected items)
- Physician signature and signature date

For items provided on a periodic basis, including drugs, the written order must include:

- Item(s) to be dispensed
- Dosage or concentration, if applicable
- Route of Administration
- Frequency of use
- Duration of infusion, if applicable
- Quantity to be dispensed
- Number of refills

For the “Date of the order” described above, use the date the supplier is contacted by the physician (for verbal orders) or the date entered by the physician (for written dispensing orders).

Frequency of use information on orders must contain detailed instructions for use and specific amounts to be dispensed. Reimbursement shall be based on the specific utilization amount only. Orders that only state “PRN” or “as needed” utilization estimates for replacement frequency, use, or consumption are not acceptable. (PIM 5.9)

The detailed description in the written order may be either a narrative description or a brand name/model number.

Signature and date stamps are not allowed. Signatures must comply with the CMS signature requirements outlined in PIM 3.3.2.4.

The DWO must be available upon request.

A prescription is not considered as part of the medical record. Medical information intended to demonstrate compliance with coverage criteria may be included on the prescription but must be corroborated by information contained in the medical record.

MEDICAL RECORD INFORMATION

GENERAL (PIM 5.7 - 5.9)

The **Indications and Limitations of Coverage and/or Medical Necessity** section of this LCD contains numerous reasonable and necessary (R&N) requirements. The **Nonmedical Necessity Coverage and Payment Rules** section of the related Policy Article contain numerous non-reasonable

and necessary, benefit category and statutory requirements that must be met in order for payment to be justified. Suppliers are reminded that:

- Supplier-produced records, even if signed by the ordering physician, and attestation letters (e.g. letters of medical necessity) are deemed not to be part of a medical record for Medicare payment purposes.
- Templates and forms, including CMS Certificates of Medical Necessity, are subject to corroboration with information in the medical record.

Information contained directly in the contemporaneous medical record is the source required to justify payment except as noted elsewhere for prescriptions and CMNs. The medical record is not limited to physician's office records but may include records from hospitals, nursing facilities, home health agencies, other healthcare professionals, etc. (not all-inclusive). Records from suppliers or healthcare professionals with a financial interest in the claim outcome are not considered sufficient by themselves for the purpose of determining that an item is reasonable and necessary.

CONTINUED USE

Continued use describes the ongoing utilization of supplies or a rental item by a beneficiary.

Suppliers are responsible for monitoring utilization of DMEPOS rental items and supplies. No monitoring of purchased items or capped rental items that have converted to a purchase is required. Suppliers must discontinue billing Medicare when rental items or ongoing supply items are no longer being used by the beneficiary.

Beneficiary medical records or supplier records may be used to confirm that a DMEPOS item continues to be used by the beneficiary. Any of the following may serve as documentation that an item submitted for reimbursement continues to be used by the beneficiary:

- Timely documentation in the beneficiary's medical record showing usage of the item, related option/accessories and supplies
- Supplier records documenting the request for refill/replacement of supplies in compliance with the Refill Documentation Requirements (This is deemed to be sufficient to document continued use for the base item, as well)
- Supplier records documenting beneficiary confirmation of continued use of a rental item

Timely documentation is defined as a record in the preceding 12 months unless otherwise specified elsewhere in this policy.

CONTINUED MEDICAL NEED

For all DMEPOS items, the initial justification for medical need is established at the time the item(s) is first ordered; therefore, beneficiary medical records demonstrating that the item is reasonable and necessary are created just prior to, or at the time of, the creation of the initial prescription. For purchased items, initial months of a rental item or for initial months of ongoing supplies or drugs,

information justifying reimbursement will come from this initial time period. Entries in the beneficiary's medical record must have been created prior to, or at the time of, the initial DOS to establish whether the initial reimbursement was justified based upon the applicable coverage policy.

For ongoing supplies and rental DME items, in addition to information described above that justifies the initial provision of the item(s) and/or supplies, there must be information in the beneficiary's medical record to support that the item continues to be used by the beneficiary and remains reasonable and necessary. Information used to justify continued medical need must be timely for the DOS under review. Any of the following may serve as documentation justifying continued medical need:

- A recent order by the treating physician for refills
- A recent change in prescription
- A properly completed CMN or DIF with an appropriate length of need specified
- Timely documentation in the beneficiary's medical record showing usage of the item.

Timely documentation is defined as a record in the preceding 12 months unless otherwise specified elsewhere in the policy.

REFILL DOCUMENTATION (PIM 5.2.5-6)

A routine refill prescription is not needed. A new prescription is needed when:

- There is a change of supplier
- There is a change in the item(s), frequency of use, or amount prescribed
- There is a change in the length of need or a previously established length of need expires
- State law requires a prescription renewal

For items that the beneficiary obtains in-person at a retail store, the signed delivery slip or a copy of the itemized sales receipt is sufficient documentation of a request for refill.

For items that are delivered to the beneficiary, documentation of a request for refill must be either a written document received from the beneficiary or a contemporaneous written record of a phone conversation/contact between the supplier and beneficiary. The refill request must occur and be documented before shipment. A retrospective attestation statement by the supplier or beneficiary is not sufficient. The refill record must include:

- Beneficiary's name or authorized representative if different than the beneficiary
- A description of each item that is being requested
- Date of refill request

- For consumable supplies, i.e., those that are used up (e.g., ostomy or urological supplies, surgical dressings, etc.) - the supplier should assess the quantity of each item that the beneficiary still has remaining, to document that the amount remaining will be nearly exhausted on or about the supply anniversary date.
- For non-consumable supplies, i.e., those more durable items that are not used up but may need periodic replacement (e.g., PAP and RAD supplies) - the supplier should assess whether the supplies remain functional, providing replacement (a refill) only when the supply item(s) is no longer able to function. Document the functional condition of the item(s) being refilled in sufficient detail to demonstrate the cause of the dysfunction that necessitates replacement (refill).

This information must be kept on file and be available upon request.

PROOF OF DELIVERY (PIM 4.26, 5.8)

Proof of delivery (POD) is a Supplier Standard and Durable Medical Equipment, Prosthetics, Orthotics, and Supplies (DMEPOS) suppliers are required to maintain POD documentation in their files. For medical review purposes, POD serves to assist in determining correct coding and billing information for claims submitted for Medicare reimbursement. Regardless of the method of delivery, the contractor must be able to determine from delivery documentation that the supplier properly coded the item(s), that the item(s) delivered are the same item(s) submitted for Medicare reimbursement and that the item(s) are intended for, and received by, a specific Medicare beneficiary.

Suppliers, their employees, or anyone else having a financial interest in the delivery of the item are prohibited from signing and accepting an item on behalf of a beneficiary (i.e., acting as a designee on behalf of the beneficiary). The signature and date the beneficiary or designee accepted delivery must be legible.

For the purpose of the delivery methods noted below, designee is defined as any person who can sign and accept the delivery of DMEPOS on behalf of the beneficiary.

Proof of delivery documentation must be available to the Medicare contractor on request. All services that do not have appropriate proof of delivery from the supplier will be denied and overpayments will be requested. Suppliers who consistently fail to provide documentation to support their services may be referred to the OIG for imposition of Civil Monetary Penalties or other administrative sanctions.

Suppliers are required to maintain POD documentation in their files. For items addressed in this policy there are two methods of delivery:

1. Delivery directly to the beneficiary or authorized representative
2. Delivery via shipping or delivery service

Method 1—Direct Delivery to the Beneficiary by the Supplier

Suppliers may deliver directly to the beneficiary or the designee. In this case, POD to a beneficiary must be a signed and dated delivery slip. The POD record must include:

- Beneficiary's name
- Delivery address
- Sufficiently detailed description to identify the item(s) being delivered (e.g., brand name, serial number, narrative description)
- Quantity delivered
- Date delivered
- Beneficiary (or designee) signature and date of signature

The date of signature on the delivery slip must be the date that the DMEPOS item was received by the beneficiary or designee. In instances where the item is delivered directly by the supplier, the date the beneficiary received the DMEPOS item must be the date of service on the claim.

Method 2—Delivery via Shipping or Delivery Service Directly to a Beneficiary

If the supplier utilizes a shipping service or mail order, the POD documentation must be a complete record tracking the item(s) from the DMEPOS supplier to the beneficiary. An example of acceptable proof of delivery would include both the supplier's own detailed shipping invoice and the delivery service's tracking information. The supplier's record must be linked to the delivery service record by some clear method like the delivery service's package identification number or supplier's invoice number for the package sent to the beneficiary. The POD record must include:

- Beneficiary's name
- Delivery address
- Delivery service's package identification number, supplier invoice number or alternative method that links the supplier's delivery documents with the delivery service's records.
- Sufficiently detailed description to identify the item(s) being delivered (e.g., brand name, serial number, narrative description)
- Quantity delivered
- Date delivered
- Evidence of delivery

If a supplier utilizes a shipping service or mail order, suppliers must use the shipping date as the date of service on the claim.

Suppliers may also utilize a return postage-paid delivery invoice from the beneficiary or designee as a POD. This type of POD record must contain the information specified above.

POLICY SPECIFIC DOCUMENTATION REQUIREMENTS

The ICD-9 code that justifies the need for these items must be included on the claim.

KX, GA, AND GZ MODIFIERS:

Suppliers must add a KX modifier to codes for an HFCWO device and accessories only if all of the criteria in the Indications and Limitations of Coverage and/or Medical Necessity section of this policy have been met.

If all of the criteria in the Indications and Limitations of Coverage and/or Medical Necessity section have not been met, the GA or GZ modifier must be added to the code. When there is an expectation of a denial as not reasonable and necessary, suppliers must enter GA on the claim line if they have obtained a properly executed Advance Beneficiary Notice (ABN) or GZ if they have not obtained a valid ABN.

There must be information in the beneficiary's medical record that describes in detail the underlying medical condition(s) that cause the accumulation of pulmonary secretions, the treatment interventions (for example, chest physiotherapy, postural drainage, medications used, mechanical modalities such as in-exsufflation devices, etc. (not all-inclusive)) and the effectiveness of the treatment. This information must be available upon request.

Claim lines billed without a KX, GA, or GZ modifier will be rejected as missing information.

MISCELLANEOUS

Refer to the Supplier Manual for more information on documentation requirements.

Appendices

PIM citations above denote references to CMS Program Integrity Manual, Internet Only Manual 100-8

Utilization Guidelines

Refer to Indications and Limitations of Coverage and/or Medical Necessity
Sources of Information and Basis for Decision

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Revision History Information

Please note: The Revision History information included in this LCD prior to 1/24/2013 will now display with a Revision History Number of "R1" at the bottom of this table. All new Revision History information entries completed on or after 1/24/2013 will display as a row in the Revision History section of the LCD and numbering will begin with "R2".

Revision History Date	Revision History Number	Revision History Explanation	Reason(s) for Change
05/01/2013	R2	Revision Effective Date: 05/01/2013 COVERAGE INDICATIONS, LIMITATIONS AND/OR MEDICAL NECESSITY:	Provider Education/Guidance

Changed: Word “Patient” to “Beneficiary”
 DOCUMENTATION REQUIREMENTS:
 (Note: The effective date above is not applicable to this section. These revised and added requirements are existing Medicare requirements which are now included in the LCD for easy reference)

Added: Standard language
 Added: Standard therapy coverage criteria documentation

01/01/2011 R1

Revision Effective Date: 01/01/2011
 INDICATIONS AND LIMITATIONS OF COVERAGE:
 Revised: Preamble language
 HCPCS CODES AND MODIFIERS:
 Revised: GA modifier

Maintenance (annual review with new changes, formatting, etc.)

Revision Effective Date: 10/01/2009
 INDICATIONS AND LIMITATIONS OF COVERAGE:
 Clarified: Coverage criterion #2
 HCPCS CODES AND MODIFIERS:
 Added: GA, GZ
 Revised: KX
 DOCUMENTATION REQUIREMENTS:
 Added: Instructions for GA and GZ modifiers

Revision Effective Date: 10/01/2008
 INDICATIONS AND LIMITATIONS OF COVERAGE:
 Added: Coverage for specified neuromuscular diseases
 Added: Statement about concurrent use of mechanical in-exsufflation device
 ICD-9 CODES THAT SUPPORT MEDICAL NECESSITY:
 Added: ICD-9 codes for neuromuscular diseases

3/1/2008 - In accordance with Section 911 of the Medicare Modernization Act, this policy was transitioned to DME MAC Noridian (19003) LCD L12739 from DME PSC Electronic Data Systems Corp. (77006) LCD L12739.

Revision Effective Date: 07/01/2007
 INDICATIONS AND LIMITATIONS OF COVERAGE:
 Removed: DMERC reference
 DOCUMENTATION REQUIREMENTS:
 Removed: DMERC references
 Removed additional documentation requirements

SOURCES OF INFORMATION AND BASIS
FOR DECISION:
Removed: References

03/01/2006 - In accordance with Section 911 of the Medicare Modernization Act of 2003, this policy was transitioned to DME PSC Electronic Data Systems Corp. (77006) from DMERC CIGNA Government Services (05655).

Revision Effective Date: 04/01/2005
LMRP converted to LCD and Policy Article.
INDICATIONS AND LIMITATIONS OF
COVERAGE AND/OR MEDICAL
NECESSITY:
Revised coverage criteria to allow for
conventional CT scan for diagnosis of
bronchiectasis

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Associated Documents

Attachments

There are no attachments for this LCD

Related Local Coverage Documents

Article(s)

[A25365 - High Frequency Chest Wall Oscillation Devices - Policy Article - Effective May 2013](#)

Related National Coverage Documents

All Versions

Updated on 03/30/2013 with effective dates 05/01/2013 - N/A

[Updated on 03/08/2012 with effective dates 01/01/2011 - 04/30/2013](#)

[Updated on 02/27/2011 with effective dates 01/01/2011 - N/A](#)

[Updated on 02/27/2011 with effective dates 01/01/2011 - N/A](#)

[Updated on 08/26/2009 with effective dates 10/01/2009 - 12/31/2010](#)

[Updated on 07/26/2009 with effective dates 10/01/2009 - N/A](#)

[Updated on 09/14/2008 with effective dates 10/01/2008 - 09/30/2009](#)

[Updated on 09/14/2008 with effective dates 10/01/2008 - N/A](#)

[Updated on 02/19/2008 with effective dates 07/01/2007 - 09/30/2008](#)

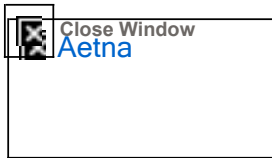
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Keywords

N/A

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Clinical Policy Bulletin:
Chest Physiotherapy and Airway Clearance Devices
Number: 0067
(Replaces CPBs 252, 280, 333)

Policy

1. Aetna considers home chest physiotherapy by a respiratory therapist medically necessary upon the initial prescription of chest physiotherapy to stabilize the member and to train family members or caregivers to administer chest physiotherapy. Chest physiotherapy by a respiratory therapist is also considered medically necessary when the member's pulmonary condition is unstable. Chest physiotherapy by a respiratory therapist is not considered medically necessary for persons whose pulmonary condition is stable, as chest physiotherapy can be competently administered at home by a family member or caregiver.
2. Aetna considers the following airway clearance devices medically necessary durable medical equipment (DME) to assist in mobilizing respiratory tract secretions for members with the conditions that are indicated below:
 1. Airway oscillating devices (e.g., Flutter and Acapella) are considered medically necessary for cystic fibrosis, bronchitis, bronchiectasis, and asthma.
 2. Mechanical percussors (e.g., Fluid Flo and Frequencer) are considered medically necessary for cystic fibrosis, chronic bronchitis, bronchiectasis, immotile cilia syndrome, and asthma.
 3. Positive expiratory pressure (PEP) mask is considered medically necessary for cystic fibrosis, chronic bronchitis, asthma, and chronic obstructive pulmonary disease.
3. Aetna considers high-frequency chest compression systems (e.g., the Frequencer, the SmartVest, the MedPulse Respiratory Vest System, the Vest Airway Clearance System, the ABI Vest, Respin11 Bronchial Clearance System, and the InCourage Vest/System) medically necessary in lieu of chest physiotherapy for the following indications, where there is a documented failure of standard treatments to adequately mobilize retained secretions:
 1. Bronchiectasis, confirmed by CT scan, characterized by daily productive cough for at least 6 continuous months or by frequent (i.e., more than 2 times/year) exacerbations requiring antibiotic therapy; *or*
 2. Cystic fibrosis; *or*

Policy History

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Effective: 10/23/1995

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3. The member has one of the following neuromuscular disease diagnoses:

1. Acid maltase deficiency
2. Anterior horn cell diseases
3. Hereditary muscular dystrophy
4. Multiple sclerosis
5. Myotonic disorders
6. Other myopathies
7. Paralysis of the diaphragm
8. Post-polio
9. Quadriplegia.

4. Lung transplant recipients, within the first 6 months post-operatively, who are unable to tolerate standard chest physiotherapy.

Aetna considers high-frequency chest compression systems experimental and investigational for other indications (e.g., alpha 1-antitrypsin deficiency, cerebral palsy, coma, kyphosis, leukodystrophy, scoliosis, and stiff-person (stiff-man) syndrome; not an all inclusive list) because their effectiveness for these indications has not been established.

4. Aetna considers mechanical in-exsufflation devices medically necessary DME for persons with a neuromuscular disease (e.g., amyotrophic lateral sclerosis, high spinal cord injury with quadriplegia) that is causing a significant impairment of chest wall and/or diaphragmatic movement and for whom standard treatments (e.g., chest percussion and postural drainage, etc.) have not been successful in adequately mobilizing retained secretions.
5. Aetna considers intrapulmonary percussive ventilators (e.g., the Impulsator F00012) experimental and investigational as there is insufficient evidence supporting their effectiveness.

Background

Cystic fibrosis (CF), chronic bronchitis, bronchiectasis, immotile cilia syndrome, asthma, and some acute respiratory tract infections can lead to abnormal airway clearance or increase sputum production. Airway secretions are cleared by mucociliary clearance (MCC), in addition to other mechanisms such as cough, peristalsis, two-phase gas-liquid flow and alveolar clearance. The underlying pathology of abnormal airway clearance differs from one illness to another. Chest physiotherapy (CPT) is a treatment program that attempts to compensate for abnormal airway clearance. By removing mucopurulent secretions, it decreases airway obstruction and its consequences, such as atelectasis and hyperinflation; furthermore, physiotherapy can decrease the rate of proteolytic tissue damage by removing infected secretions. Methods to improve removal of tenacious lung secretions in patients with CF contribute to slowing the decline in respiratory function.

The standard dependent method of pulmonary care remains clapping, vibration and compression, together with postural drainage and assisted coughing. Most practitioners prescribe 20 to 30-min CPT sessions 1 to 3 times a day, depending on the severity of disease and the presence of intercurrent infection.

Respiratory therapists can teach family members or other informal caregivers to competently administer manual CPT to children and others who are incapable of doing it for themselves. The National Heart Lung and Blood Institute (1995) of the National Institutes of Health states: "Chest therapy consists of bronchial, or postural, drainage, which is done by placing the patient in a position that allows drainage of the mucus from the lungs. At the same time, the chest or back is clapped (percussed) and vibrated to dislodge the mucus and help it move out of the airways.

This process is repeated over different parts of the chest and back to loosen the mucus in different areas of each lung. This procedure has to be done for children by family members but older patients can learn to do it by themselves. Mechanical aids that help chest physical therapy are available commercially."

Different types of airway clearance devices have been developed for independent use, which require little or no assistance by others. When a competent care giver is not available to administer CPT manually, specific alternative methods may be utilized. Many of these techniques have been developed and studied using CF patients.

De Boeck and colleagues (2008) noted that airway clearance techniques are an important part of the respiratory management in children with CF, bronchiectasis and neuromuscular disease. They are also, however, frequently prescribed in previously healthy children with an acute respiratory problem with the aim to speed up recovery. These investigators reviewed the evidence behind this use of airway clearance techniques in children without underlying disease. They stated that few studies have been performed; many different techniques are available and the therapies used are often poorly specified. It is necessary to name the specific airway clearance technique used in treatment rather than to just state "chest physiotherapy," a term that is often confused with chest clapping or vibration plus postural drainage. There is little evidence that airway clearance techniques play a role in the management of children with an acute respiratory problem. Physicians routinely prescribing airway clearance techniques in previously healthy children should question their practice.

High Frequency Chest Compression Systems

A high-frequency chest wall compression device (The Vest Airway Clearance System, formerly known as the ThAIRapy Vest, ABI Vest) (Advanced Respiratory, St. Paul, MN) is an inflatable vest connected to a compressor that provides external high-frequency chest wall oscillation. The vest is connected via tubing to an air pulse delivery system. The patient then uses a foot pedal to apply pressure pulses that cause the vest to inflate and deflate against the thorax creating an oscillatory or vibratory motion.

High-frequency chest compression devices have been shown to increase sputum production in CF patients. Cystic fibrosis is caused by abnormal chloride ion transport on the apical surface of epithelial cells in exocrine gland tissues. The abnormally composition of secretions from affected epithelial surfaces results in increased viscosity. It has been theorized that high-frequency chest compression devices are particularly effective in clearing the abnormal secretions of CF because vibratory shear forces facilitate expectoration by reducing the viscosity of these secretions, much in the same way that shaking jello causes it to become fluid. However, high-frequency chest compression vests have not been proven to be more effective than manual chest physiotherapy. It can be used in place of manual chest physiotherapy for patients with CF where manual chest physiotherapy is unavailable.

High-frequency chest wall compression devices have been promoted for use in conditions other than CF, including non-CF bronchiectasis. However, there are no adequate published controlled clinical studies of high-frequency chest compression devices for conditions other than CF. Given the unique pathophysiology of CF resulting in the abnormal composition of CF secretions, evidence of the effectiveness of high-frequency chest wall compression devices in CF can not be extrapolated to other pulmonary conditions. The Vest was cleared by the Food and Drug Administration (FDA) for a wide variety of pulmonary conditions based on a 510(k) pre-market notification; thus the manufacturer was not required to submit the type of evidence of effectiveness that would be required to support a pre-market approval (PMA) application.

In addition, there are no adequate studies comparing high-frequency chest compression to other, relatively simple and substantially less expensive devices (e.g., Flutter, Acapella) that apply high-frequency oscillation to the airway.

The American College of Chest Physicians' evidence-based clinical practice guidelines on non-pharmacologic airway clearance therapies (McCool and Rosen, 2006) recommend oscillatory devices (e.g., Flutter, IPV, and HFCWO) be considered as an alternative to chest physiotherapy only in CF patients.

The Vest is only available for purchase (it can not be rented); the air pulse delivery system (an air-pulse generator) and flexible hoses are available for rental or purchase.

There is controversy surrounding the use of high-frequency chest physiotherapy devices for indications other than CF.

Yuan and colleagues (2010) stated that airway secretions and infections are common in cerebral palsy (CP) and neuromuscular diseases. Chest physiotherapy is standard therapy but effort is substantial. High-frequency chest wall oscillation (HFCWO) is used in CF, but tolerability and safety data in cerebral palsy and neuromuscular disease are limited. These researchers performed a prospective, randomized, controlled trial of HFCWO and standard CPT in patients with neuromuscular disease or CP. Outcome measures included respiratory-related hospitalizations, antibiotic therapy, chest radiographs, and polysomnography. Caregivers were questioned regarding therapy adherence. A total of 28 participants enrolled, 23 completed (12 CPT, mean study period 5 months). No adverse outcomes were reported. Adherence to prescribed regimen was higher with HFCWO ($p = 0.036$). These findings suggest safety, tolerability, and better compliance with HFCWO. Improvement in airway clearance may help prevent hospitalizations. The authors noted that larger controlled trials are needed to confirm these results.

Drosman and Jones (2005) noted that, in the pediatric population, HFCWO is most widely used in children with CF, but that children with developmental disorders involving neuromuscular dysfunction also have impaired airway clearance with or without ventilatory dependence. The authors stated that "[l]arge, long-term studies are needed examining HFCC in the patients with developmental disorders."

In an "exploratory" randomized controlled trial, Lange et al (2006) assessed changes in respiratory function in patients with amyotrophic lateral sclerosis (ALS) after using HFCWO. This was a 12-week study of HFCWO in patients with probable or definite ALS, an Amyotrophic Lateral Sclerosis Functional Rating Scale respiratory subscale score less than or equal to 11 and greater than or equal to 5, and forced vital capacity (FVC) greater than or equal to 40 % predicted. A total of 46 patients

were enrolled (58.0 +/- 9.8 years; 21 men, 25 women); 22 used HFCWO and 24 were untreated. Only 35 completed the trial: 19 used HFCWO and 16 untreated. Results were reported per-protocol, rather than by intention-to-treat. HFCWO users had less breathlessness ($p = 0.021$) and coughed more at night ($p = 0.048$) at 12 weeks compared to baseline. At 12 weeks, HFCWO users reported a decline in breathlessness ($p = 0.048$); non-users reported more noise when breathing ($p = 0.027$). There were no significant differences in FVC change, peak expiratory flow, capnography, oxygen saturation, fatigue, functional quality of life, or transitional dyspnea index. When patients with FVC between 40 and 70 % predicted were analyzed, FVC showed a significant mean decrease in untreated patients but not in HFCWO patients; HFCWO patients had significantly less increased fatigue and breathlessness. Satisfaction with HFCWO was 79 %. The authors concluded that HFCWO was well-tolerated, considered helpful by a majority of patients, and decreased symptoms of breathlessness. In patients with impaired breathing, HFCWO decreased fatigue and showed a trend toward slowing the decline of forced vital capacity. The investigators explained that the study was exploratory in nature, and was not sufficiently powered to detect significant differences in clinical outcomes such as pulmonary complications, hospitalizations or mortality.

On the other hand, Chaisson et al (2006) did not find HFCWO to be of significant help to patients with ALS. These investigators evaluated the effectiveness of HFCWO administered through the Vest Airway Clearance System when added to standard care in preventing pulmonary complications and prolonging the time to death in patients with ALS. A total of 9 patients with a diagnosis of ALS and concurrently receiving non-invasive ventilatory support with bi-level positive airway pressure (BiPAP) were recruited from an outpatient clinic. Four patients were randomized to receive standard care and 5 patients to receive standard care plus the addition of HFCWO administered twice-daily for 15-min duration. Longitudinal assessments of oxyhemoglobin saturation, forced FVC, and adverse events were obtained until time of death. Pulmonary complications of atelectasis, pneumonia, hospitalization for a respiratory-related abnormality, and tracheostomy with mechanical ventilation were monitored throughout the study duration. No differences were observed between treatment groups in relation to the rate of decline in FVC. The addition of HFCWO airway clearance failed to improve time to death compared to standard treatment alone (340 days +/- 247 versus 470 days +/- 241; $p = 0.26$). The random allocation of HFCWO airway clearance to patients with ALS concomitantly receiving BiPAP failed to attain any significant clinical benefits in relation to either loss of lung function or mortality. This study does not exclude the potential benefit of HFCWO in select patients with ALS who have co-existent pulmonary diseases, pre-existent mucus-related pulmonary complications, or less severe levels of respiratory muscle weakness.

The Frequencer (Dymedso, Inc., Boisbriand, Quebec, Canada) is a device that provides airway clearance therapy and promotes bronchial drainage by inducing vibration in the chest walls. It induces oscillatory sound waves in the chest by means of an electro-acoustical transducer (referred to as the "Power Head"), which is placed externally on the user's chest. The Power Head is connected to a frequency generator that is capable of producing frequencies between 20 and 100 Hz, and induces sound waves in the user's chest for the purpose of loosening mucus deposits.

The Frequencer device provides airway clearance by inducing oscillatory sound waves in the chest by means of an electro-acoustical transducer placed externally on the patient's chest. The transducer is connected to a frequency generator which is capable of producing frequencies between 20 and 100Hz. The vibrations in the

patient's chest are effective in loosening mucus deposits and promoting bronchial drainage. The Frequencer consists of two parts, a control unit and a transducer. The user places the transducer on the chest. The frequency (adjustable between 20 and 100HZ) and the volume are adjusted in the control unit to create sympathetic resonance that can be felt in the lungs. According to the manufacturer, there are significant differences between other high frequency percussors and the Frequencer. Specifically: (1) other devices deliver a frequency pounding or striking action, similar to clapping, to a patient's chest to loosen mucus. The Frequencer uses a different operating principle: higher frequency acoustic waves to excite resonance in the chest. (2) Acoustic wave action makes the Frequencer appropriate patients who are: under 3 years of age; elderly and fragile; agitated; immobilized; obese; and status/post surgery.

Cantin et al (2006) stated that clearance of mucus from airways is the cornerstone of therapy for lung disease in patients with CF. These investigators described the operation of the Frequencer, a novel respiratory physiotherapy device comprised of an electro-acoustical transducer. They hypothesized that the Frequencer would be a safe and effective therapy to help clear secretions from the airways of subjects with CF. A total of 22 individuals with CF were recruited to this study comparing sputum production during conventional chest physiotherapy (CCPT) and Frequencer therapy using a cross-over design. The sputum weight was the main outcome measure. Sputum weight was found to be a reproducible measure of the efficacy of chest physiotherapy in individual patients. The Frequencer induced airway clearance in patients with CF that was equivalent to that of CCPT. Furthermore, treatment of a 4 % mucin preparation ex-vivo with the Frequencer significantly reduced the viscosity of the mucin solution as determined in a capillary rheometer. The authors concluded that these results indicated the Frequencer is safe and as effective as CCPT in inducing airway clearance in patients with CF.

Although clinical evidence is limited, high-frequency chest wall oscillation devices have been used for lung transplant recipients who are unable to tolerate standard chest physiotherapy in the post-operative period.

Mechanical Percussors

The purpose of percussion is to apply kinetic energy to the chest wall and lung at regular intervals. Percussion is also referred to as cupping, clapping, and tapotement. It can be accomplished by rhythmically striking the thorax with a cupped hand or a mechanical device applied directly over the lung segment(s) being drained. According to the guidelines developed by American Association for Respiratory Care (AARC) on postural drainage therapy, no convincing evidence demonstrates the superiority of one method over the other; however, use of a mechanical percussor can benefit the patient by allowing for independence and greater compliance.

Flutter and Acapella

The Flutter (Scandipharm, Birmingham, AL) is a handheld pipe-like device with a plastic mouthpiece on one end that the patient exhales into. On the other end of the pipe, a stainless steel ball rests inside a plastic circular cone. When the patient exhales into the device, the ball rolls and moves up and down, creating an opening and closing cycle over a conical canal. The cycle repeats itself many times throughout each exhalation intending to produce oscillations of endobronchial pressure and expiratory airflow that will vibrate the airway walls and loosen mucus so that it can be easily expectorated by the patient. The Flutter device has 510(k)

status with the FDA. Although the Flutter device has not been shown to significantly change respiratory assessment parameters or pulmonary function, some patients may prefer this method over other therapies.

A similar oscillatory positive airway pressure device, the Acapella (Smiths Medical, Watford, UK), uses a counterweighted plug and magnet to create air flow oscillation. Volsko et al (2003) noted that the Acapella and Flutter have similar performance characteristics. The author noted that the Acapella's performance is not gravity-dependent (i.e., dependent on device orientation) and may be easier to use for some patients.

Positive Expiratory Pressure (PEP)

The PEP mask/mouthpiece contains a valve that increases resistance to expiratory airflow. The patient breathes in and out 5 to 20 times through the flow resistor, creating positive pressure in the airways during exhalation. The pressure generated can be monitored and adjusted with a manometer. Either low pressures or high pressures are prescribed. The PEP mask/mouthpiece achieves the same goal as autogenic drainage (a special breathing technique aimed at avoiding airway compression by reducing positive expiratory transthoracic pressure) by expiring against an external airflow obstruction.

Most studies on the effectiveness of PEP have been conducted in Europe and they reported short-term equivalency of PEP to other methods of airway clearance. A published review of these studies found that PEP had similar effects on sputum clearance when compared with other methods (postural drainage forced exhalatory technique). The strongest evidence of the effectiveness of PEP comes from a 1-year randomized controlled clinical trial of PEP versus conventional physiotherapy in 40 children with CF. The patients treated with PEP showed improvements in pulmonary function, whereas pulmonary function actually declined in patients treated with conventional physiotherapy. The differences between treatment groups were statistically significant for changes in FVC and FEV1.

There are numerous PEP Mask/PEP Valves on the market. Examples include: Resistex PEP Mask (Mercury Medical, Clearwater, FL), TheraPep Valve (DHD Healthcare, Inc., Canastota, NY), Acapella (DHD Healthcare, Inc., Wampsville, NY) and PARI PEP Mask (PARI Respiratory Equipment, Inc., Midlothian, VA).

Intrapulmonary Percussive Ventilator (IPV)

Intrapulmonary Percussive Ventilator (IPV) (Percussionaire Corporation, Sandpoint, ID) is an aerosol machine that delivers a series of pressurized gas minibursts at rates of 100 to 225 cycles/min to the respiratory tract. Aerosolized medications can be delivered under pressure and with oscillations that vibrate the chest. In contrast to PEP and flutter, IPV allows continuous monitored positive pressure application and percussion throughout the respiratory cycle. The patient controls variables such as inspiratory time, peak pressure and delivery rates. The Percussionaire has 510(k) status with the FDA.

There is a scarcity of scientific data to support the effectiveness of IPV. A small study (n = 16) by Homnick et al (1995) found IPV as effective as standard aerosol and chest physiotherapy in preserving lung function. A study by Newhouse et al (1998) concluded that larger and longer studies of IPV compared to standard chest physiotherapy are needed to evaluate its value for independent administration of chest physiotherapy. Studies do not demonstrate any advantage of IPV over that

achieved with good pulmonary care in the hospital environment and there are no studies in the home setting.

Reychler et al (2006) stated that IPV, frequently coupled with a nebulizer, is increasingly used as a physiotherapy technique. However, its physiological and clinical values have been poorly studied. These researchers compared lung deposition of amikacin by the nebulizer of the IPV device and that of standard jet nebulization (SJN). Amikacin was nebulized with both devices in a group of 5 healthy subjects during spontaneous breathing. The deposition of amikacin was measured by urinary monitoring. Drug output of both devices was measured. Respiratory frequency (RF) was significantly lower when comparing the IPV device with SJN (8.2 ± 1.6 breaths/min versus 12.6 ± 2.5 breaths/min, $p < 0.05$). The total daily amount of amikacin excreted in the urine was significantly lower with IPV than with SJN (0.8 % initial dose versus 5.6 % initial dose, $p < 0.001$). Elimination half-life was identical with both devices. Drug output was lower with IPV than with SJN. The amount of amikacin delivered to the lung is 6-fold lower with IPV than with SJN, although a lower RF was adopted by the subjects with the IPV. The authors concluded that the IPV seems unfavorable for the nebulization of antibiotics.

Brückner (2008) stated that assisted coughing and mechanical cough aids compensate for the weak cough flow in patients with neuromuscular diseases (NMD). In cases with preserved respiratory muscles, breathing techniques and special devices (e.g., Flutter or Acapella) can be used for secretion mobilization during infections of the airways. These physiotherapeutic approaches were summarized as oscillating physiotherapy. Their mechanisms are dependent on separation of the mucus from the bronchial wall by vibration, thus facilitating mucus transport from the peripheral to the central airways. In mucoviscidosis and chronic obstructive pulmonary disease their application is established, but there is a paucity of data regarding the commitment in patients with NMD. The effective adoption of simple oscillating therapeutic interventions demands usually a sufficient force of the respiratory muscles -- exceptions are the application of the Percussionaire (i.e., IPV) or high-frequency chest wall oscillation (HFCWO). In daily practice there is evidence that patients with weak respiratory muscles are overstrained with the use of these approaches, or get exhausted. A general recommendation for the adoption of simple oscillating physiotherapeutic interventions can not be made in patients with NMD. Perhaps in the future devices such as IPV or HFCWO will prove to be more effective in patients with NMD.

The Impulsator F00012 (Percussionaire Corp, Sandpoint, ID) is an intra-pulmonary percussive ventilator; it is a pneumatic device that delivers high-flow-rate bursts of air and aerosol to the lungs at a frequency of 200 to 300 cycles per minute. Pulsatile breaths are delivered at a peak pressure of 20 to 40 cm H₂O, titrated by visualizing percussive movement of the intercostal spaces. Breathes are delivered using a mouthpiece, and the lungs percussed for 5- to 15-second intervals over a 15- to 30-min period. There is a lack of evidence regarding the effectiveness of the Impulsator F00012.

Mechanical Insufflation-Exsufflation

Mechanical insufflation-exsufflation (CoughAssist, J.H. Emerson Co., Cambridge, MA) (also known as In-Exsufflator, Coughlator, cough machine) is designed to inflate the lung with positive pressure and assist cough with negative pressure; it is advocated for use in patients with NMD. The published literature on the effectiveness of mechanical insufflation-exsufflation consists of review articles,

case reports, retrospective analyses, and small, uncontrolled case series. In addition, published research on mechanical insufflation-exsufflation has come from a single investigator, raising questions about the generalization of findings. A Consensus Panel Report by the American College of Chest Physicians (Irwin et al, 1998) stated that "[t]he inability of patients with respiratory muscle weakness to achieve high lung volumes is likely to contribute to cough ineffectiveness. Increasing the inhaled volume prior to cough by air-stacking positive pressure breaths or by glossopharyngeal breathing increases cough expiratory flows by 80 % in these patients. Cough efficiency may be further enhanced by the application of negative pressure to the airway for a period of 1 to 3 s. Using this technique of mechanical insufflation-exsufflation, peak cough expiratory flows can be increased by more than four-fold." The Consensus Panel Report, however, concluded that "[w]hile a variety of nonpharmacologic protussive treatment modalities may improve cough mechanics, clinical studies documenting improvement in patient morbidity and mortality are lacking."

Motivation to perform any airway clearance technique is key to maintaining pulmonary function. An increase in sputum production, while not necessarily an indicator of improved pulmonary function, motivates most patients to continue with their physiotherapy treatment. The ease in which the therapy can be performed by a particular patient is another important consideration. Most adolescent and adult patients who need chest physiotherapy are able to carry out their treatment independently with one of the above methods and using gravity assisted positions and breathing exercises. Positive expiratory pressure mask/mouthpiece and the Flutter device are well accepted by children. Long-term comparison of these methods with large groups of patients including the selection of appropriate outcome measures, are needed for further evaluation of the potential success of various methods of airway clearance.

CPT Codes / HCPCS Codes / ICD-9 Codes

Home Chest Physiotherapy:

CPT codes covered if selection criteria are met:

94667, 94668

97124

HCPCS codes covered if selection criteria are met:

G0237 Therapeutic procedures to increase strength or endurance of respiratory muscles, face-to-face, one-on-one, each 15 minutes (includes monitoring)

G0238 Therapeutic procedures to improve respiratory function, other than described by G0237, one-on-one, face-to-face, per 15 minutes (including monitoring)

ICD-9 codes covered if selection criteria are met:

277.00 - Cystic fibrosis
277.09

335.20 - Motor neuron disease
335.29

344.00 - Quadriplegia and quadriplegia
344.09

358.0 - 359.9	Myoneural disorders
490 - 496	Chronic obstructive pulmonary disease and allied conditions
519.4	Disorders of diaphragm
748.61	Congenital bronchiectasis
805.00 - 806.39	Fracture of vertebral column, cervical or dorsal [thoracic]
907.2	Late effect of spinal cord injury
907.3	Late effect of injury to nerve root(s), spinal plexus(es), and other nerves of trunk
952.00 -952.19	Spinal cord injury without evidence of spinal bone injury, cervical or dorsal [thoracic]
V42.6	Organ or tissue replaced by transplant, lung

Airway Clearance Devices:

High-frequency chest compression systems:

HCPCS codes covered if selection criteria are met:

A7025	High frequency chest wall oscillation system vest, replacement for use with patient owned equipment, each
A7026	High frequency chest wall oscillation system hose, replacement for use with patient owned equipment, each
E0483	High frequency chest wall oscillation air-pulse generator system, (includes hoses and vest), each

ICD-9 codes covered if selection criteria are met:

011.50 - 011.56	Tuberculous bronchiectasis
138	Late effects acute poliomyelitis
277.00 - 277.09	Cystic fibrosis
335.0 - 335.9	Anterior horn cell disease
340	Multiple sclerosis
344.00 - 344.09	Quadriplegia and quadriparesis
359.0 - 359.1	Congenital hereditary and hereditary progressive muscular dystrophy
359.21 - 359.29	Myotonic disorders
359.4 - 359.6	Toxic myopathy, myopathy in endocrine diseases classified elsewhere, and symptomatic inflammatory myopathy in diseases classified elsewhere
359.89	Other myopathies
494.0 - 494.1	Bronchiectasis
519.4	Disorders of diaphragm [paralysis of the diaphragm]

748.61 Congenital bronchiectasis
 V42.6 Organ or tissue replaced by transplant, lung

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

333.91 Stiff-Man Syndrome
 343.0 - 343.9 Infantile cerebral palsy
 737.0 Adolescent postural kyphosis
 737.10 - Kyphosis (acquired)
 737.19
 737.30 - Kyphoscoliosis and scoliosis
 737.39
 737.41, 737.43 Kyphosis or scoliosis associated with other conditions
 754.2 Congenital musculoskeletal deformities of spine
 780.01 Coma

Mechanical Percussors:

HCPCS codes covered if selection criteria are met:

E0480 Percussor, electric or pneumatic, home model

ICD-9 codes covered if selection criteria are met:

277.00 - Cystic fibrosis
 277.09
 491.0 -491.9 Chronic bronchitis
 493.00 -493.92 Asthma
 494.0 - 494.1 Bronchiectasis
 748.61 Congenital bronchiectasis
 V42.6 Organ or tissue replaced by transplant, lung

Flutter / Acapella Device:

HCPCS codes covered if selection criteria are met:

S8185 Flutter device

ICD-9 codes covered if selection criteria are met:

277.00 - Cystic fibrosis
 277.09
 491.0 - 491.9 Chronic bronchitis
 494.0 - 494.1 Bronchiectasis
 748.61 Congenital bronchiectasis
 493.00 - Asthma
 493.92
 V42.6 Organ or tissue replaced by transplant, lung

Positive Expiratory Pressure (PEP):

HCPCS codes covered if selection criteria are met:

E0484 Oscillatory positive expiratory pressure device, non-electric, any type, each

ICD-9 codes covered if selection criteria are met:

277.0 - 277.09 Cystic fibrosis

490 - 496 Chronic obstructive pulmonary disease and allied conditions

Mechanical Insufflation-Exsufflation Devices:

HCPCS codes covered if selection criteria are met:

A7020 Interface for cough stimulating device, includes all components, replacement only

E0482 Cough stimulating device, alternating positive and negative airway pressure

ICD-9 codes covered if selection criteria are met:

335.20 - Motor neuron disease
335.29

344.00 - Quadriplegia and quadriplegia
344.09

358.0 - 359.9 Myoneural disorders

519.4 Disorders of diaphragm

805.00 - Fracture of vertebral column, cervical or dorsal [thoracic]
806.39

907.2 Late effect of spinal cord injury

907.3 Late effect of injury to nerve root(s), spinal plexus(es), and other nerves of trunk

952.00 - Spinal cord injury without evidence of spinal bone injury,
952.19 cervical or dorsal [thoracic]

Intrapulmonary percussive ventilators (IPV):

HCPCS codes not covered for indications listed in the CPB:

E0481 Intrapulmonary percussive ventilation system and related accessories

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Therapeutic ultrasound for venous leg ulcers (Review)

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[Intervention Review]

Therapeutic ultrasound for venous leg ulcers

Nicky Cullum¹, Deyaa Al-Kurdi², Sally EM Bell-Syer³

¹ School of Nursing, Midwifery and Social Work, University of Manchester, Manchester, UK. ² The Cochrane Wounds Group, University of York, York, UK. ³ Department of Health Sciences, University of York, York, UK

Contact address: Nicky Cullum, School of Nursing, Midwifery and Social Work, University of Manchester, Jean McFarlane Building, Oxford Road, Manchester, M13 9PL, UK. nicky.cullum@manchester.ac.uk.

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ABSTRACT

Background

Venous leg ulcers pose a significant burden for patients and healthcare systems. Ultrasound (US) may be a useful treatment for these ulcers.

Objectives

To determine whether US increases the healing of venous leg ulcers.

Search methods

We searched the Cochrane Wounds Group Specialised Register (searched 24 February 2010); The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 1, 2010); Ovid MEDLINE (1950 to February Week 2 2010); In-Process & Other Non-Indexed Citations (searched 24 February 2010); Ovid EMBASE 1980 to 2010 Week 07; EBSCO CINAHL 1982 to 24 February 2010.

Selection criteria

Randomised controlled trials (RCTs) comparing US with no US.

Data collection and analysis

Two authors independently assessed the search results and selected eligible studies. Details from included studies were summarised using a data extraction sheet, and double-checked. We tried to contact trial authors for missing data.

Main results

Eight trials were included; all had unclear, or high, risks of bias, with differences in duration of follow-up, and US regimens. Six trials evaluated high frequency US and five of these reported healing at 7 - 8 weeks. Significantly more patients healed with US than without it at 7 - 8 weeks (pooled RR 1.4, 95% CI 1.0 to 1.96), but later assessments at 12 weeks showed the increased risk of healing with US was no longer statistically significant (pooled RR 1.47, 95% CI 0.99 to 2.20). One poor-quality study of high-frequency US found no evidence of an effect on healing after three weeks' treatment.

Two trials evaluated low frequency US and reported healing at different time points. Both trials reported no evidence of a difference in the proportion of ulcers healed with US compared with no US: both were significantly underpowered.

Authors' conclusions

The trials evaluating US for venous leg ulcers are small, poor-quality and heterogeneous. There is no reliable evidence that US hastens healing of venous ulcers. There is a small amount of weak evidence of increased healing with US, but this requires confirmation in larger, high-quality RCTs. There is no evidence of a benefit associated with low frequency US.

PLAIN LANGUAGE SUMMARY

Ultrasound therapy used for healing venous (varicose) leg ulcers and to improve symptoms

Venous leg ulcers are common, especially in the elderly. They are caused by damage or blockages in the veins of the legs, which in turn lead to pooling of blood and increased pressure in these veins. Eventually, these changes can damage the skin and lead to ulcer formation.

Compression with stockings or bandages is the most widely used, and acceptable, treatment for venous leg ulcers. Ultrasound has been used as an additional intervention, especially for difficult, long-standing ulcers. The mechanisms by which ultrasound waves interact with healing tissues are not fully understood. We conducted a review to establish whether ultrasound speeds the healing and improve symptoms of venous leg ulcers, and examined all the available evidence from medical trials. This showed that there is no strong evidence that ultrasound hastens ulcer healing. There is, however, some weak evidence from poor-quality research that high-frequency ultrasound may increase the healing of venous leg ulcers. This finding, however, requires confirmation in larger and rigorously conducted medical trials before we can be certain that it is true and can be trusted. There is no evidence that low frequency ultrasound improves the healing of venous leg ulcers.

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Low-Frequency Ultrasound (20-40 kHz) as an Adjunctive Therapy for Chronic Wound Healing: A Systematic Review of the Literature and Meta-Analysis of Eight Randomized Controlled Trials

Jeffrey Voigt, MBA, MPH¹, Martin Wendelken, DPM, RN²,
Vickie Driver, MS, DPM, FACFAS³, and Oscar M. Alvarez, PhD⁴

Abstract

Ultrasound as a therapeutic agent in chronic wound healing has been studied extensively. This systematic review and meta-analysis specifically examines low-frequency (20-30 kHz) ultrasound delivered at either low or high intensity. The objective of this review was to determine whether low-frequency ultrasound used as an adjunctive therapy improves the outcomes of complete healing and reduction of size of chronic lower limb wounds. PubMed, Cochrane/CENTRAL, technical assessment, relevant wound-related journals, and clinical guidelines were searched along with contacting manufacturers and authors of relevant randomized controlled trials were completed. Searches focused on the use of low-frequency ultrasound in randomized controlled trials. Data were collected via a data collection form and was adjudicated independently via coauthors. Meta-analyses and heterogeneity checks were performed using Mantel–Haenszel and inverse variance (fixed and random effects) statistical methods on studies with similar outcomes (complete healing and percent wound area reduction) over similar time periods. Single study results were reported via the statistical methods used in the study. Eight randomized controlled trials were identified. Results demonstrated that early healing (at ≤5 months) in patients with venous stasis and diabetic foot ulcers was favorably influenced by both high- and low-intensity ultrasound delivered at a low frequency—either via contact or noncontact techniques. However, the quality of the data may be suspect, especially for low-frequency low-intensity noncontact ultrasound because of significant biases. In patients presenting with either venous stasis or diabetic foot ulcers (Wagner classification 1-3), early healing appears to be facilitated by either low-frequency low-intensity noncontact ultrasound or low-frequency high-intensity contact ultrasound.

Keywords

Low frequency ultrasound, chronic wound healing, wound debridement

Chronic recalcitrant lower extremity wounds (pressure ulcers, arterial insufficiency ulcers, venous leg ulcers, diabetic foot ulcers, burns) are wounds that have failed to proceed through an orderly and timely reparative process to produce anatomic and functional integrity, or proceeded through the repair process without establishing a sustained anatomic and functional result.¹ There are numerous recommended treatment modalities for the healing of these types of wounds, including debridement (eg, with scalpel, autolytic, enzymatic, mechanical [wet to dry technique], laser, maggot therapy, high-pressure water jet), dressings, compression therapy, and drug therapy to improve the blood flow in patients with circulatory problems.²⁻¹⁰ Ultrasound as a primary therapy has been studied and evaluated in Cochrane Reviews¹¹ and has been shown not to have an

effect on healing when compared with sham or to the combination of ultrasound along with ultraviolet light. However, it was noted that the possibility of a beneficial or harmful effect could not be ruled out because of the small number of trials (4) and the small numbers of participants

¹Medical Device Consultants of Ridgewood, LLC, Ridgewood, NJ, USA

²Center for Curative and Palliative Wound Care, Calvary Hospital, Bronx, NY, 10461

³Boston University School of Medicine, Boston Medical Center, Boston, MA, 02118

⁴Department of Medicine, New York Medical College, Valhalla, NY, 10595.

Corresponding Author:

Jeffrey Voigt, Medical Device Consultants of Ridgewood, LLC, 99
Glenwood Road, Ridgewood, NJ 07450, USA
Email: meddevconsultant@aol.com



Coverage Guideline

Subject: Low-Frequency Ultrasound Therapy for Wound Management
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Status: Reviewed **Last Review Date:** 11/08/2012

Description/Scope

This document addresses the use of low-frequency, non-contact, non-thermal ultrasound therapy for wound management.

Note: Please see the following related document for additional information:

- [DME.00009 Vacuum Assisted Wound Therapy in the Outpatient Setting](#)

Position Statement

Investigational and Not Medically Necessary:

Use of low-frequency, non-contact, non-thermal, ultrasound therapy is considered **investigational and not medically necessary** for all applications.

Rationale

To date, there is limited clinical trial evidence regarding use of low-frequency, non-contact, non-thermal, ultrasound therapy. One such article describes a sham-controlled, randomized, double-blinded, multicenter study conducted in hospital-based and private wound care clinics of 55 individuals. The "therapy" was either active 40 KHz ultrasound delivered by a saline mist or a sham device which delivered a saline mist without the use of ultrasound. At 12 weeks of care, results showed that the group who had received the ultrasound therapy had an increase in the healing rate for recalcitrant diabetic foot ulcers, compared to control (40.7% vs. 14.3%). However, it was noted that five of the 23 treatment centers had not been doing the treatment protocol correctly, and, for this reason, these individuals were not considered evaluable. The results of this study suggest the need for further research, including assessment of the impact of quantitative biopsy results at enrollment, debridement depth and impact on healing, as well as the potential antimicrobial action of this ultrasound device (Ennis, 2005).

In a prospective, randomized controlled trial, Kavros and colleagues (2007a) assigned 35 individuals with non-healing leg and foot ulcers, due to chronic critical limb ischemia, to standard wound care, and another 35 to standard care plus low-frequency, non-contact, non-thermal ultrasound therapy. After 12 weeks, 63% of individuals in the active treatment group achieved at least 50% wound healing, as compared with 29% in the standard care group. In addition, individuals in either group with transcutaneous oxygen pressure less than 20 mm Hg were much less likely to achieve significant healing.

Kavros and colleagues (2007b) also described an open-label, nonrandomized, baseline-controlled, single-center clinical case series conducted at the Gonda Vascular Wound Healing Center at the Mayo Clinic. Fifty-one individuals presenting to this wound center with chronic non-healing wounds of the lower leg or foot of three to 18 months duration were included in the study. Individuals' comorbidities or prior failure in ulcer therapy did not exclude them from this feasibility study, including the confirmed presence of osteomyelitis. A large proportion of the study participants had a component of limb ischemia and diabetes mellitus (n = 38). Sixty five percent (65%) of the study subjects had transcutaneous oximetry levels less than 30 mm Hg, and 22% had levels less than 20 mm Hg. Fourteen (14) individuals had positive deep culture findings with *Staphylococcus aureus* and *Pseudomonas aeruginosa* being the most common pathogens identified. All individuals first received the standard of care protocol followed by the ultrasound therapy when the investigator determined that the wounds were no longer progressing. Study results demonstrated a significant improvement in the rate of healing during the ultrasound therapy time period, compared with the time period when conventional standard wound care alone was administered, with reduction in wound volume of 37.3% in the standard care group and 94.9% in the noncontact low frequency ultrasound group. The authors acknowledge that some degree of bias was possible, due to the baseline-controlled study design, and that further clinical and basic science study of this technology is warranted.

Another author commented about the challenges of conducting randomized controlled trials of wound healing noting that, "In general, designing clinical studies for wound healing is difficult, and surrogate endpoints might enable trials to be constructed with valid outcomes measures, other than total closure. Many randomized controlled clinical wound care studies have failed to deliver the outcomes anticipated by pre-

clinical work, an observation that warrants further study on the need for better methods of quantifying the debridement process, in order to accurately compare study results" (Margolis 2004).

A Cochrane review (Cullum, 2010) concluded that "there is no reliable evidence that US hastens healing of venous ulcers" and "There is no evidence of a benefit associated with low frequency US." The National Institute for Health and Clinical Excellence (NICE) published medical technology guidance in 2011 which does not support the routine use of low-frequency ultrasound for wound therapy.

At the present time, the published evidence is insufficient to demonstrate the safety and efficacy of low-frequency ultrasound therapy for wound care management, as compared to conventional treatment options.

Background/Overview

The MIST Therapy® System (Celleration, Inc. Eden Prairie, MN) is an ultrasound wound cleaning system that received 510(k) marketing clearance from the U.S. Food and Drug Administration (FDA) in June 2004 and a second FDA clearance in May 2005. The FDA classified this device as a Class II device that is considered to be substantially equivalent to other devices of this generic type, i.e., low-energy, ultrasound wound cleanser devices. However, this FDA approval is subject to special controls (contained within the Class II Special Controls Guidance Document issued Nov. 7, 2005). According to the FDA, "The special controls document aids in mitigating the risk by establishing performance characteristics, safety testing, and appropriate labeling." The MIST Therapy System is FDA cleared for prescription use only, at this time, and is indicated to promote wound healing through wound cleansing and maintenance debridement through the removal of yellow slough, fibrin, tissue exudates and bacteria. Potential risks to health that may be associated with this device were identified by the FDA as: delayed wound healing, thermal damage, inflammation/foreign body response, infection and electrical shock (FDA, 2005). Since the marketing clearance of the MIST Therapy System, other similar devices have also received FDA 510(k) clearance and list the MIST Therapy System as the predicate device.

Definitions

The MIST Therapy System: This device consists of an equipment component (an ultrasonic generator and transducer) and a disposable component (sterile applicator). The sterile disposable applicator is attached to the generator's transducer and has been designed to accept a pre-packaged sterile bottle of saline. Generally, treatment consists of three sessions per week, during which time the nurse or therapist holds the device near the wound while ultrasonic energy generated by the device atomizes the saline and delivers a continuous mist to the treatment site. The disposable applicator contains an on/off valve that controls the flow of sterile saline to the ultrasound transducer surface. This device is designed to deliver low levels of ultrasound energy to the wound bed by means of the generated mist without direct contact of the device with the wound, thereby avoiding possible contamination.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. A draft of future ICD-10 Coding (effective 10/01/2014) related to this document, as it might look today, is included below for your reference. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:

For the following procedure code for all indications or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

0183T Low frequency, non-contact, non-thermal ultrasound, including topical application (s) when performed, wound assessment, and instruction(s) for ongoing care; per day

ICD-9 Diagnosis

All diagnoses

ICD-10 Diagnosis ICD-10-CM draft codes; effective 10/01/2014:

All diagnoses

References

Peer Reviewed Publications:

1. Bell AL, Cavorsi J. Noncontact ultrasound therapy for adjunctive treatment of nonhealing wounds: retrospective analysis. *Phys Ther*. 2008; 88(12): 1517-1524.
2. Ennis WJ, Foremann P, Mozen N, et al. Ultrasound therapy for recalcitrant diabetic foot ulcers: results of a randomized double-blind controlled multicenter study. *Ostomy Wound Manage*. 2005; 51(8): 24-39.
3. Ennis WJ, Valdes W, Gainer M, Meneses P. Evaluation of clinical effectiveness of MIST ultrasound therapy for the healing of chronic wounds. *Adv Skin Wound Care*. 2006; 19(8): 437-446.
4. Gehling ML, Samies JH. The effect of noncontact, low-intensity, low-frequency therapeutic ultrasound on lower-extremity chronic wound pain: A retrospective chart review. *Ostomy Wound Manage*. 2007; 53(3): 44-50.
5. Hinchliffe RJ, Valk GD, Apelqvist J, et al. A systematic review of the effectiveness of interventions to enhance the healing of chronic ulcers of the foot in diabetes. *Diabetes Metab Res Rev*. 2008; 24 Suppl 1: S119-S144.
6. Kavros SJ, Liedl DA, Boon AJ, et al. Expedited wound healing with noncontact, low-frequency ultrasound therapy in chronic wounds: a retrospective analysis. *Adv Skin Wound Care*. 2008; 21(9): 416-423.
7. Kavros SJ, Miller JL, Hanna SW. Treatment of ischemic wounds with non-contact, low-frequency ultrasound: the Mayo Clinic experience, 2004-2006. *Adv Skin Wound Care*. 2007a; 20(4): 221-226.
8. Kavros SJ, Schenck EC. Use of noncontact low-frequency ultrasound in the treatment of chronic foot and leg ulcerations: a 51-patient analysis. *J Am Podiatr Med Assoc*. 2007b; 97(2): 95-101.
9. Margolis D. The swings and roundabouts of randomized controlled studies in wound healing. *Lower Extremity Wounds*. 2004; 3(1): 4-6.
10. Ramundo J, Gray M. Is ultrasonic mist therapy effective for debriding chronic wounds? *J Wound Ostomy Continence Nurs*. 2008; 35(6): 579-583.
11. Samies J, Gehling M. Acoustic pressure wound therapy for management of mixed partial- and full-thickness burns in a rural wound center. *Ostomy Wound Manage*. 2008; 54(3): 56-59.
12. Serena T. Wound closure and gradual involution of an infantile hemangioma using a noncontact, low-frequency ultrasound therapy. *Ostomy Wound Manage*. 2008; 54(2): 68-71.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Akbari Sari A, Flemming K, Cullum NA, Wollina U. Therapeutic ultrasound for pressure ulcers. *Cochrane Database Syst Rev*. 2006; (3):CD001275.
2. American Society of Plastic Surgeons (ASPS). Evidence-based clinical practice guideline: Chronic wounds of the lower extremity. 2007. Available at: <http://www.plasticsurgery.org/Documents/medical-professionals/health-policy/evidence-practice/Evidence-based-Clinical-Practice-Guideline-Chronic-Wounds-of-the-Lower-Extremity.pdf>. Accessed on July 30, 2012.
3. Cullum NA, Al-Kurdi D, Bell-Syer SEM. Therapeutic ultrasound for venous leg ulcers. *Cochrane Database Syst Rev*. 2010; (6):CD001180.
4. Frykberg RG, Zgonis T, Armstrong DG, et al. Diabetic foot disorders: A clinical practice guideline. *J Foot Ankle Surg*. 2006; 45(5):S2-S66. Available at: http://www.acfas.org/uploadedFiles/Healthcare_Community/Education_and_Publications/Clinical_Practice_Guidelines/DiabeticCPG-small.pdf. Accessed on July 30, 2012.
5. Institute for Clinical Systems Improvement (ICSI). Health Care Protocol: Pressure ulcer treatment. Third Edition, January 2012. Available at: http://www.icsi.org/pressure_ulcer_treatment_protocol_review_and_comment/pressure_ulcer_treatment_protocol.html. Accessed on July 27, 2012.
6. National Institute for Health and Clinical Excellence. Medical technology guidance 5. The MIST Therapy system for the promotion of wound healing, July 2011. Available at: <http://www.nice.org.uk/nicemedia/live/13548/55637/55637.pdf>. Accessed on July 27, 2012.
7. U.S. Food and Drug Administration 510(k) Premarket Notification Database. Celleration MIST Therapy System Summary of Safety and Effectiveness. No. K032378. Rockville, MD: FDA. June 25, 2004. No. K050129. May 2005. Available at: http://www.accessdata.fda.gov/cdrh_docs/pdf5/K050129.pdf. Accessed on July 30, 2012.

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MIST Therapy System
 Quoustic Wound Therapy System™
 Sonoca 180/185 Wound Care System
 Ultrasound, low-frequency wound therapy
 Wound management, ultrasound MIST therapy

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

Document History

Status	Date	Action
Reviewed	11/08/2012	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Rationale and References.
Reviewed	11/17/2011	MPTAC review. Updated Rationale, Background/Overview, References, and Index. Removed Web Sites for Additional Information.
Reviewed	11/18/2010	MPTAC review. Description, Rationale, Background/Overview, References and Index updated.
Reviewed	11/19/2009	MPTAC review. No change to stance. References were updated.
Reviewed	11/20/2008	MPTAC review. No change to stance. References were updated.
New	11/29/2007	MPTAC review. Initial document development.

Section 5.0

Biennial review

Fibromyalgia

Question: should Fibromyalgia be given higher priority on the Prioritized List?

Question source: National Fibromyalgia and Chronic Pain Association

Issue: Fibromyalgia is located on Line 634 DISORDERS OF SOFT TISSUE, which is below the current funding line. The placement and coverage of fibromyalgia was last reviewed in May 2008. Previous review was in 2000. During both of these reviews, the HSC did not find that the available treatments for fibromyalgia were effective. Those treatments which were thought to be effective, such as analgesics and antidepressants, were felt to be adequately covered elsewhere on the List.

From the May, 2008 HOSC minutes:

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The HOSC heard testimony from Dr. Bennett, a rheumatologist at OHSU who reported multiple conflicts of interest, including funding from Merck, Berringer, Pfizer, and other pharmaceutical companies. Dr. Bennett testified about the prevalence of fibromyalgia, its effects on quality of life, and the high health care utilization of fibromyalgia patients. He then reviewed accepted treatments.

Jennifer Wagner from the DHS and the Governor's office also spoke as an advocate for pain patients. She stressed how important this issue was from both patients and providers prospective.

Smits reviewed the current evidence on effectiveness of various treatments for fibromyalgia. DMAP input on restrictions for treatment for fibromyalgia was elicited. Shaffer noted that the PA for Neurontin is being eliminated, but a PA was being instituted for Lyrica. HOSC members briefly discussed whether the HSC would need to make a guideline regarding treatments covered for fibromyalgia if fibromyalgia is moved above current funding line.

Olson pointed out that the HSC covers office visits and most medications for the coverage of fibromyalgia currently, despite the placement of fibromyalgia below the current funding line. Shaffer responded that in FFS Medicaid, fibromyalgia is a below the line diagnosis and therefore providers are not paid for office visits for this diagnosis. Saha pointed out that the evidence for effectiveness of the current medications is not strong; therefore coverage of such medications would not be evidence based. Gubler raised concerns that prevalence of the disease outstrips the disease prevalence (i.e. fibromyalgia is overdiagnosed). Dr. Bennett did not feel that fibromyalgia is overdiagnosed, and noted that most Rheumatologists and Psychiatrists, as well as well-educated primary care physicians, are able to make the diagnosis.

Dodson wondered what would the HSC move below the line to make room for moving fibromyalgia above the line. McKelvey pointed out that the major benefit of moving fibromyalgia is access to medications, and the evidence for the effectiveness of these medications is lacking. Olson agreed and stated that the HSC needed to keep the bar high, otherwise the HSC will have many arguments about other conditions with weak effectiveness that should be covered.

Fibromyalgia

The final decision was to maintain fibromyalgia on its current line with no guideline or other change.

Evidence summary 2014 review (see full evidence summary at end of document):

- 1) Effective therapies
 - a. Exercise
 - b. Antidepressants
 - i. SNRIs, SSRIs
- 2) Possibly effective therapies
 - a. Analgesics, other than opioids
 - b. Acupuncture
 - i. Low to moderate evidence of short term efficacy
 - c. Cyclobenzaprine (Flexeril)
 - a. Modestly effective initially based on 1 meta-analysis reviewed in 2008
 - a. Gabapentin (Neurontin)
 - a. Modest decrease in pain scores vs. placebo at 12 weeks in 1 small RCT reviewed in 2008
 - b. Pregabalin (Lyrica)-- reviewed in 2008
 - a. Modest effectiveness which appears transient
 - c. Cognitive behavioral therapy
 - d. Patient education
 - e. Balneotherapy (heated pool therapy/hydrotherapy)
- 3) No evidence of effectiveness
 - a. Multi-disciplinary rehabilitation
 - b. Non-acupuncture CAM treatments
 - c. Biofeedback
 - a. PT/OT
 - b. Relaxation therapy
 - c. Trigger point injections
 - d. MAOIs
 - e. Amitriptyline
 - f. Clonazepam
 - g. Phenytoin
 - h. Botulinum toxin
- 4) Probably harmful
 - a. Opiates

Recommendation:

- 1) Keep fibromyalgia on Line 634
 - a. Therapies with good evidence of effectiveness (antidepressants, analgesics other than opiates) are covered for other indications and are available to patients
 - i. Exercise has good evidence of effectiveness but is not covered for any indication on the Prioritized List currently
 - b. Other therapies (acupuncture, pool therapy, cognitive behavioral therapy) with possible effectiveness would not be covered
 - c. Some medications could be subject to PA and not covered

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Evidence Review (2008, updated 2013)

General Treatment Recommendations

- 1) **EULAR 07** (European League Against Rheumatism) systematic review and treatment guidelines [reviewed in 2008]
 - a. 146 studies, most small and of short duration and many of poor quality
 - b. Only balneotherapy and strength training had an effect size for pain or function 95% confidence interval which did not cross zero
 - i. All medications CI crossed zero
 - c. Recommendations
 - i. Heated pool therapy with or without exercise is beneficial
 1. 5 trials
 2. SOE (strength of evidence): B
 - ii. Exercise can be beneficial for some patients
 1. Expert opinion
 2. 11 studies, most of limited to poor quality
 3. Conflicting results
 4. SOE: C
 - iii. Cognitive behavioral therapy can be beneficial for some patients
 1. Expert opinion and 2 poor quality trials
 2. SOE: D
 - iv. Tramadol is effective for treatment of pain in fibromyalgia
 1. 2 RCTs, longest 13 weeks duration
 2. SOE: A
 - v. Antidepressants: amitriptyline, fluoxetine, duloxetine, milnacipran, moclobemide and pirlindole, reduce pain and often improve function
 1. 5 trials, 4 with positive outcomes
 2. SOE: A
 - vi. Tropicisetron, pramipexole and pregabalin reduce pain
 1. 1 trial reported for each
 2. SOE: A
 - vii. Simple analgesics such as paracetamol and other weak opioids can also be considered in the treatment of fibromyalgia. Corticosteroids and strong opioids are not recommended
 1. SOE: D
- 2) **Goldenberg 04**: Literature review and treatment guidelines [reviewed in 2008]
 - a. Strong Evidence for Efficacy
 - i. Amitriptyline (3 RCTs)
 - ii. Cyclobenzaprine (3 RCTs)
 - iii. Cardiovascular exercise: efficacy not maintained if exercise stops.
 - iv. Cognitive Behavioral Therapy: improvement often sustained for months
 - v. Patient education: group format using lectures, written materials, demonstrations; improvement sustained for 3 to 12 months.
 - vi. Multidisciplinary therapy, such as exercise and CBT or education and exercise.
 - b. Modest Evidence for Efficacy
 - i. Tramadol
 - ii. Serotonin reuptake inhibitors (SSRIs):
 1. Fluoxetine (only one carefully evaluated at this time)

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- iii. Dual-reuptake inhibitors (SNRIs):
- iv. Venlafaxine: 1 RCT ineffective but 2 case reports found higher dose effective.
- v. Milnacipran: effective in single RCT
- vi. Duloxetine: effective in single RCT
- vii. Pregabalin: second-generation anticonvulsant; effective in single RCT.
- viii. Strength training
- ix. Acupuncture
- x. Hypnotherapy
- xi. Biofeedback
- xii. Balneotherapy.
- c. Weak Evidence for Efficacy
 - i. Growth hormone
 - ii. 5-Hydroxytryptamine (serotonin): methodological problems.
 - iii. S-adenosyl-methionine: mixed results.
 - iv. Chiropractic, manual, and massage therapy
 - v. Electrotherapy
 - vi. Ultrasound
- d. No Evidence for Efficacy
 - i. Opioids, corticosteroids, nonsteroidal anti-inflammatory drugs, benzodiazepine and nonbenzodiazepene hypnotics, melatonin, calcitonin, thyroid hormone, guaifenesin, dehydroepiandrosterone, magnesium.
 - ii. Tender (trigger) point injections
 - iii. Flexibility exercise

Exercise therapy

- 1) Cochrane review of exercise (2009)
 - a. 2276 subjects in 34 studies (1264 assigned to exercise interventions)
 - b. "Moderate quality evidence that aerobic-only exercise training at recommended intensity levels has positive effects global well-being (SMD 0.44, 95% confidence interval (CI) 0.13 to 0.75) and physical function (SMD 0.68, 95% CI 0.41 to 0.95) and possibly on pain (SMD 0.94, 95% CI -0.15 to 2.03) and tender points (SMD 0.26, 95% CI -0.28 to 0.79). Strength and flexibility remain underevaluated."
 - c. "There is 'gold' level evidence (www.cochranemsk.org) that supervised aerobic exercise training has beneficial effects on physical capacity and FMS symptoms."

Medications

- 2) Cochrane review of NSAIDs, analgesics and opioids
 - a. Protocol published February 2012
- 3) SNRIs
 - a. Duloxetine (Cochrane 2011)
 - i. Duloxetine at 60 mg daily is also effective in fibromyalgia over 12 weeks (RR 50% reduction in pain 1.57, 95% CI 1.20 to 2.06; NNT 8, 95% CI 5 to 17) and 28 weeks (RR 1.58, 95% CI 1.10 to 2.27).
 - b. Milnacipran (Savella) (Cochrane 2012)
 - i. 5 studies (N=4138), good quality

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- ii. Both doses of milnacipran provided moderate levels of pain relief to about 40% of those treated, compared to 30% with placebo, giving a number needed to treat of 8 to 10.
 - iii. "The evidence available indicates that milnacipran 100 mg or 200 mg is effective for a minority in the treatment of pain due to fibromyalgia, providing moderate levels of pain relief (at least 30%) to about 40% of participants, compared with about 30% with placebo. There were insufficient data to assess substantial levels of pain relief (at least 50%), and the use of last observation carried forward imputation may overestimate drug efficacy. Milnacipran is associated with increased adverse events and adverse event withdrawals, which were significantly greater for the higher dose."
- 4) O'Mally 00: Systematic review of Antidepressants [reviewed in 2008]
- a. 13 studies included in review
 - i. 9 trials with tricyclics
 - ii. 9 trials with SSRIs
 - iii. 3 trials with SAM-e
 - b. Improvement OR 4.2 (2.6-6.8)
 - i. Improvement in sleep, fatigue, pain, well-being improved
 - ii. No improvement in trigger points
 - iii. NNT for symptom improvement=4
 - iv. Regression analysis found no differences by drug class
 - v. "Antidepressants are efficacious at treating many of the symptoms of fibromyalgia...whether this effect is independent of depression needs further study."
- 5) Tofferi 04: meta-analysis of cyclobenzaprine [reviewed in 2008]
- a. 5 fair-quality RCTs
 - b. OR for global improvement with therapy=3.0 (95% confidence interval [95% CI] 1.6 –5.6)
 - c. NNT= 4.8 (95% CI 3.0–11) individuals needing treatment for 1 patient to experience symptom improvement.
 - d. Small to moderate effect in pain and sleep compared to placebo in first 12 weeks
 - e. Pain improved early on, but there was no improvement in fatigue or tender points at any time.
- 6) Arnold 07: RCT of treatment with gabapentin (Neurontin) [reviewed in 2008]
- a. N=150
 - b. At 12 weeks, mean decrease in pain scores of 2 points for active group vs. 1 point for placebo group
 - c. 51% of active group had at least a 30% reduction in pain at 12 weeks compared to 31% with placebo group
 - d. "Gabapentin (1,200–2,400 mg/day) is safe and efficacious for the treatment of pain and other symptoms associated with fibromyalgia."
- 7) Medical Letter 07: review of evidence for pregabalin (Lyrica) [reviewed in 2008]
- a. 3 RCTs (N=529, 745, 566)
 - i. In an 8-week trial in 529 patients with fibromyalgia, >50% reduction in mean pain scores at the end of the trial occurred in 29% of patients with pregabalin 150 mg tid and in 13% with placebo, a statistically significant difference; no significant difference was detected between placebo and pregabalin 50 mg tid or 100 mg tid.

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1. Crofford 05 (see below)
 - ii. In a 14-week double-blind trial, among 745 patients who had not responded to placebo during a 1-week “run-in” period, >30% improvement in pain scores occurred in 42% of those taking pregabalin 150 mg bid, in 50% with pregabalin 225 mg bid, 48% with pregabalin 300 mg bid and in 30% with placebo. All doses of the drug were significantly superior to placebo.
 1. Published in abstract form only to date
 - iii. In a randomized withdrawal study (FREEDOM), 566 patients with fibromyalgia who had a >50% reduction in mean pain scores with the drug were randomized to continue pregabalin or switch to placebo for 26 weeks. By the end of the study, 32% of those who had continued pregabalin and 61% of those switched to placebo had lost their therapeutic response.
 1. Crofford 08 (see below)
 - b. “Pregabalin (Lyrica) appears to be modestly, and sometimes transiently, effective in reducing pain in patients with fibromyalgia.”
- 8) Crofford 05: Pregabalin RCT [reviewed in 2008]
- a. Pfizer funded study
 - b. 8 week multi-center trial
 - c. N=529 (398 active, 131 placebo)
 - d. Reduction in pain score: about -1 for placebo and -2 for active. No significant differences in pain between placebo and active at 8 weeks
 - e. -0.93 reduction in pain score between 450 mg of pregabalin (but not lower doses) and placebo at “end point” (intent to treat, last observation carried forward analysis)
 - f. Significant improvement in sleep between study and placebo at 8 weeks
 - g. The proportion of patients classified as responders (>50% improvement from baseline) at end point was significantly greater in the 450 mg/day pregabalin group (28.9%), but not in the 300 (18.9%) or 150 (13.0%) mg/day pregabalin groups, compared with the placebo group (13.2%)
- 9) Crofford 08: Pregabalin RCT [reviewed in 2008]
- a. Pfizer funded study
 - b. Initial 6 week open label trial; patients who responded to medication were then enrolled in a 6 month durability trial and re-randomized to pregabalin or placebo
 - c. 1777 screened, 1051 entered open label trial, 566 completed OL and met inclusion criteria (287 placebo, 279 pregabalin), 162 (55 placebo, 107 drug) patients completed six month trial
 - d. Primary endpoint was loss of treatment response (LTR), <30% reduction in pain score relative to baseline (VAS score based on 100mm scale)
 - e. 32% of pregabalin group vs. 61% of placebo group reached LTR by end of 6 month double blind trial
 - i. 39% of placebo group maintained treatment response despite being randomized off drug
 - f. Questions with methodology
 - i. “last observation carried forward:” when a patient dropped out or was lost to follow up, the last pain score was carried forward (rather than survival analysis)
 - ii. Many patients “censored” out of trial

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- g. "In those who respond, pregabalin demonstrated durability of effect for relieving FM pain"
- 10) Mease 08: Pregabalin RCT [reviewed in 2008]
 - a. Pfizer funded study
 - b. Slightly higher dosages than the Crofford studies (300mg lowest dose)
 - c. 13 week
 - d. 1328 screening, 748 randomized (558 drug vs 190 placebo); 263 withdrew from the study (35%)
 - e. Results: decrease in pain score (on 0-10 scale) of 0.44 (300mg vs placebo); 0.47 (600mg vs placebo), and 0.66 (600mg vs placebo)
 - f. Results: improvement in sleep and patient impression of global improvement vs. placebo
 - i. Sleep quality improved 0.86 to 1.21 on a 0-10 scale vs. placebo
 - ii. FIQ (Fibromyalgia Impact Questionnaire) not significantly different between drug and placebo
 - g. Questions with methodology
 - i. "last observation carried forward:" when a patient dropped out or was lost to follow up, the last pain score was carried forward (rather than survival analysis)
 - h. Authors conclusion: "pregabalin was efficacious and safe for treatment of pain associated with fibromyalgia"
- 11) Botulinum toxin
 - a. Cochrane 2012
 - i. 4 studies (N=233) identified. In one study with 145 participants, a significant improvement rate of pain intensity scores, as shown by the mean difference (MD) of -0.23 (95%confidence interval (CI) - 0.26 to -0.20; P value < 0.00001) and duration of daily pain (MD- 1.11; 95%CI -1.37 to -0.85; P value < 0.00001), was demonstrated when comparing BTXA with placebo. The three other studies showed that there was no statistically significant difference between BTXA and placebo in pain intensity.
 - b. "There is inconclusive evidence to support the use of botulinum toxin in the treatment of MPS"
- 12) MAOIs
 - a. Cochrane 2012
 - i. Data suggest that the effectiveness of MAOIs for the treatment of FM symptoms is limited. Although we observed a moderate effect size on pain and a small one on tender points, these results should be taken with caution as they are only based on two studies with a small number of patients and inconsistent risk of bias among them.
- 13) Amitriptyline
 - a. Cochrane 2012
 - i. Combining the classic neuropathic pain conditions of PDN, postherpetic neuralgia (PHN) and post-stroke pain with fibromyalgia for second-tier evidence, in eight studies and 687 participants, there was a statistically significant benefit (risk ratio (RR) 2.3, 95% confidence interval (CI) 1.8 to 3.1) with a number needed to treat (NNT) of 4.6 (3.6 to 6.6). The analysis showed that even using this potentially biased data, only about 38% of

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participants benefited with amitriptyline and 16% with placebo; most participants did not get adequate pain relief.

14) Clonazepam

- a. Cochrane 2013
 - i. This review uncovered no evidence of sufficient quality to support the use of clonazepam in chronic neuropathic pain or fibromyalgia

15) Phenytoin

- a. Cochrane 2013
 - i. This review uncovered no evidence of sufficient quality to support the use of phenytoin in chronic neuropathic pain or fibromyalgia

Acupuncture/CAM

16) Cochrane review 2013

- a. 9 trials (N=395), 6 of manual acupuncture (MA) and of electroacupuncture (EA)
- b. Low quality evidence from one study (13 participants) showed EA improved symptoms with no adverse events at one month following treatment.
- c. Moderate quality evidence from six studies (286 participants) indicated that acupuncture (EA or MA) was no better than sham acupuncture, except for less stiffness at one month.
- d. Low-quality evidence from one study suggested that MA group resulted in poorer physical function
- e. Moderate quality evidence from one study (58 participants) found that compared with standard therapy alone (antidepressants and exercise), adjunct acupuncture therapy reduced pain at one month after treatment: mean pain was 8 points on a 0 to 10 point scale in the standard therapy group; treatment reduced pain by 3 points (95% CI -3.9 to -2.1), an absolute reduction of 30% (21% to 39%).
- f. Low quality evidence from one study (38 participants) showed a short-term benefit of acupuncture over antidepressants in pain relief:
- g. Four studies reported no differences between acupuncture and control or other treatments described at six to seven months follow-up.
- h. No serious adverse events were reported, but there were insufficient adverse events to be certain of the risks.

17) CMS Technology Review 03: Acupuncture [reviewed in 2008]

- a. 1 high quality RCT (N=70) with electroacupuncture
 - i. Significant benefits found
 - ii. Pts only followed for 3 weeks
- b. 2 low quality RCTs and several nonrandomized studies found
- c. "There is insufficient evidence to conclude that acupuncture has efficacy for the treatment of fibromyalgia."

18) Mayhew 07: Systematic review of acupuncture [reviewed in 2008]

- a. 5 RCTs of mixed/low quality (N=30-100)
 - i. 3 found short lived benefit
 - ii. 2 found no benefit
 - iii. All positive RCTs used electro-acupuncture.
 - iv. "The notion that acupuncture is an effective symptomatic treatment for fibromyalgia is not supported by the results from

Fibromyalgia

rigorous clinical trials. On the basis of this evidence, acupuncture cannot be recommended for fibromyalgia.”

- 19) Holdcraft 03: Systematic review of CAM treatments [reviewed in 2008]
- a. Summary: some evidence to support use of acupuncture, other therapies such as massage are promising. Other CAM interventions have limited evidence
 - b. Acupuncture
 - i. 2 good quality RCTs identified (N=70,60)
 - ii. Significant improvement in pain threshold in acupuncture group vs. control
 - iii. Both had limitations in blinding and no long-term follow up
 - c. Homeopathy
 - i. 1 poor quality RCT identified
 - d. Herbal/vitamin supplements
 - i. “Most studies of nutritional supplements have small sample sizes, and poor quality designs lacking randomization, placebo controls or double blinding. Thus, the empirical evidence is very limited or insufficient for most nutritional supplements.”
 - e. Dietary modification
 - i. “Overall, the evidence for dietary modifications is limited and they cannot be recommended as effective treatments for FMS based on current evidence.”
 - f. Magnet therapy
 - i. 2 small well-designed RCTs reported conflicting results
 - g. Chiropractic
 - i. “The evidence for a therapeutic benefit of chiropractic treatment is insufficient”
 - h. Massage
 - i. 2 RCTs identified (N=48,?)
 - ii. 1 study with 15 patients assigned to massage found a self-reported reduction in pain in 85% of the patients and a reduction in analgesic use by 30% of subjects.
 - iii. Other study showed improved mobility and a trend for decreased perceived helplessness when compared with control, but no impact on pain, depression, well-being and other functioning was noted, and all effects became non-significant after 28 weeks.
 - iv. “Limitations in both studies include high drop-out rates, the choice of control groups which preclude blinding to the intervention, and a single practitioner offering massage in the second study. While two RCTs suggest that massage has some positive impact, only moderate evidence (level B) exists to recommend this CAM modality to FMS patients.”
 - i. Relaxation
 - i. 1 study (N=56), guided imagery and relaxation vs. physician visit
 - ii. Pain measures over 4 weeks improved significantly only in the pleasant imagery group.
 - iii. No blinding
 - j. Biofeedback.
 - i. 1 RCT (N=12)
 - ii. Tenderpoint indices were significantly lower among subjects receiving exercise and biofeedback than among controls.

Fibromyalgia

- iii. "Taken together, the evidence is limited for the use of biofeedback with FMS."

20) Non-acupuncture CAM treatments

- a. DeSilva 2010
 - i. 7 studies (4 on various CAMs, 3 on homeopathy)
 - ii. There is insufficient evidence on any CAM, taken orally or applied topically, for FM.

Other treatment modalities

21) Cognitive behavioral therapy

- a. Bernardy 2010
 - i. 14 trials (N=910)
 - ii. There was no significant effect on pain, fatigue, sleep, and HRQOL at posttreatment and at followup.
 - iii. There was a significant effect on self-efficacy pain posttreatment (SMD 0.85, 95% CI 0.25, 1.46; $p = 0.006$) and at followup (SMD 0.90, 95% CI 0.14, 1.66; $p = 0.02$).
 - iv. Operant behavioral therapy significantly reduced the number of physician visits at followup (SMD -1.57 , 95% CI -2.00 , -1.14 ; $p < 0.001$).
 - v. Conclusion. CBT can be considered to improve coping with pain and to reduce depressed mood and healthcare-seeking behavior

22) Heated pool therapy

- a. Langhorst 2009
 - i. 10 RCTs (N=446)
 - ii. There is moderate evidence that hydrotherapy has short-term beneficial effects on pain and HRQOL in FMS patients. There is a risk to over-estimate the effects of hydrotherapy due to methodological weaknesses of the studies and to small trials included in meta-analysis Cochrane review of non-invasive physical treatments

23) Cochrane review of multidisciplinary rehabilitation (2009)

- a. 7 studies met inclusion criteria and none were considered methodologically high quality
- b. Limited or no benefits seen
- c. "We conclude that there appears to be little scientific evidence for the effectiveness of multidisciplinary rehabilitation for these musculoskeletal disorders."



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June 13, 2013

Dr. Som Saha, HERC Chair
HERC Members/Staff
Members of Oregon Health Authority Board
500 Summer Street, NE, E-20
Salem, OR 97301-1097

Jan Chambers
President & Founder

Sharon Waldrop
Vice-President for
Education

Tom Hintz
Vice-President for
Support

Dear Dr. Saha, Members of HERC and Oregon Health Authority Board,

Fibromyalgia, a very serious and life-altering chronic pain illness, affects approximately 10 million Americans, or 2-4 percent of the population.¹ We are concerned about the 117,000 Oregonians (3 percent) who have fibromyalgia (FM), many of whom utilize the Oregon Health Plan (Medicaid) and are unable to access care because FM is presently not covered on Oregon's Prioritized List of Health Services. The State of Oregon is a true outlier as the only state in America not covering fibromyalgia. Since it was last reviewed, additional scientific research evidence, understanding, expert opinion and defined evidence-based guidelines around the disease articulate the toll on patients' suffering and the impact on health system costs.^{2,3,4,5,9}

The major symptoms of fibromyalgia include multifocal pain, fatigue, sleep disturbances, and cognitive or memory problems. Other symptoms may include psychological distress, impaired functioning, and sexual dysfunction.^{6,8,9} For the first time, fibromyalgia will have its own ICD 10 code (M79.7), effective October 2014. **We respectfully request (1) a formal review of fibromyalgia to place fibromyalgia above the funding line for conditions currently being covered by the Oregon Health Plan, and (2) time on the appropriate agenda, either with (i) HERC on August 8, 2013; (ii) Evidence-based Guidelines Subcommittee on September 12, 2013; or (iii) the Value-based Benefits Subcommittee on August 8, 2013, to engage in dialogue and present the evidence about the personal, financial, and societal costs of fibromyalgia.**

We appreciate the inclusive mission of the Oregon Health Authority and the Coordinated Care Organization's Triple Aim for better health, and better care at lower costs. This fits right in with why we want to talk with you about changing the coverage of fibromyalgia. Fibromyalgia is a chronic disease with evidence-based guidelines, and patients suffer at the same or greater magnitude versus other musculoskeletal and/or debilitating conditions.^{2,6} Early diagnosis and effective treatment of fibromyalgia saves money;^{2,7,10} improves functionality and productivity;^{7,9} and reduces personal suffering, the impact on families and communities, and long-term disability.^{2,7,9} Not treating or under-treatment drives utilization and costs.^{7,9,11} Moreover, treating individual FM symptoms under different diagnostic codes in a piecemeal fashion does not result in best outcomes for management of the overall serious and debilitating nature of this condition.

As of April 2013 women comprised the majority (64 percent) of Oregon's adult Medicaid beneficiaries,¹³ many of whom are single mothers. Fibromyalgia is more prominent in women than men,^{7,10,11} and the patients who most reduced their healthcare costs were actively employed.⁷ Active management of fibromyalgia increases functionality and reduces the number of days missed at work, increasing work force productivity.^{7,9} Preventing fibromyalgia symptoms from advancing from mild to moderate to severe by early diagnosis and treatment reduces direct costs, indirect costs, and societal costs.^{8,9} We believe the negative impact on children in homes is significant where fibromyalgia is untreated and advances in severity. The prestigious Institute of Medicine *Relieving Pain in America* report (June, 2011) found that life-cycle factors (birth to adulthood) associated with the development of chronic pain in adulthood included a child's low socioeconomic status combined with parents' pain exposure and reactions.¹²

After carefully reviewing the Health Evidence Resource Commission criteria for topic reviews, we feel that we have sufficient evidence that meets the criteria at least to a minimum to warrant a serious discussion and consideration as an agenda item on an August 8th (or September 12th) meeting. We understand that these coverage decisions are challenging. They need to be prioritized. We understand the complex scoring system that determines the prioritized list rankings, and we understand that you want to make an objective determination. We strongly believe in the evidence addressing each component of that scoring criteria methodology. We wouldn't be coming to you if we didn't feel confident that we are addressing the challenges. The fact that the Oregon Health Authority has limited resources is the very reason why we encourage you to grant this request to be on the appropriate agenda, given all of the evidence around effectively managing this condition.

We look forward to working with you on this request. Please let us know if you need any clarification. We would welcome discussion in person, live on the telephone, or whatever form of communication works best for you. Please see the attached evidence referenced citations for your review.

Sincerely yours,

Jan Favero Chambers, President/Founder
National Fibromyalgia & Chronic Pain Association (jan.chambers@fmcpcaware.org)

Christopher Alftine, M.D., Medford, Oregon (Alftinec@medfordmd.com)

Robert Bennett, MD, FRCP, FACP, MACR, Professor of Medicine and Nursing at Oregon Health & Science University (bennetrobl@comcast.net)

Amy Carmona, BSN, RN-BC, CHPN: American Society of Pain Educators, Board Certified in Pain Management, Hospice and Palliative Nursing, Member, Oregon Pain Management Commission, and Prescription Opioid Poisoning Workgroup. (amy@cw3.com)

Cheryl Hryciw, F.N.P., West Linn Spine Center, West Linn, Oregon (hryciwc@aim.com)

Kim D. Jones, R.N.C., Ph.D., F.N.P., Associate Professor of Nursing, Oregon Health & Science University School of Nursing Portland Campus; Fibromyalgia Research & Treatment Team; President, Fibromyalgia Information Foundation (joneskim@ohsu.edu)

Dr. Som Saha
June 13, 2013
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Genevra Liptan, M.D., Medical Director, Good Samaritan Internal Medicine Teaching Clinic
(dr.ginevra@mac.com)

Carrie McLaughlin, M.S.N., F.N.P., Rheumatology Clinic, Oregon Health & Science University
(mclaugca@ohsu.edu)

Jennifer M Wagner, LPN, ASN, BS, Executive Director, Western Pain Society
(jennifer@painsociety.com)

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Exercise for treating fibromyalgia syndrome (Review)

Busch AJ, Barber KA, Overend TJ, Peloso PMJ, Schachter CL



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Exercise for treating fibromyalgia syndrome (Review)

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[Intervention Review]

Exercise for treating fibromyalgia syndrome

Angela J Busch¹, Karen A.R. Barber², Tom J Overend³, Paul Michael J Peloso⁴, Candice L Schachter⁵

¹School of Physical Therapy, University of Saskatchewan, Saskatoon, Canada. ²Continuing Physical Therapy Education, University of Saskatchewan, Saskatoon, Canada. ³School of Physical Therapy, University of Western Ontario, London, Canada. ⁴Basking Ridge, NJ, USA. ⁵Windsor, Canada

Contact address: Angela J Busch, School of Physical Therapy, University of Saskatchewan, 1121 College Drive, Saskatoon, Saskatchewan, S7N 0W3, Canada. angela.busch@usask.ca.

Editorial group: Cochrane Musculoskeletal Group.

Publication status and date: Edited (no change to conclusions), published in Issue 4, 2008.

Review content assessed as up-to-date: 16 August 2007.

Citation: Busch AJ, Barber KA, Overend TJ, Peloso PMJ, Schachter CL. Exercise for treating fibromyalgia syndrome. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No.: CD003786. DOI: 10.1002/14651858.CD003786.pub2.

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ABSTRACT

Background

Fibromyalgia (FM) is a syndrome expressed by chronic widespread body pain which leads to reduced physical function and frequent use of health care services. Exercise training is commonly recommended as a treatment. This is an update of a review published in Issue 2, 2002.

Objectives

The primary objective of this systematic review was to evaluate the effects of exercise training including cardiorespiratory (aerobic), muscle strengthening, and/or flexibility exercise on global well-being, selected signs and symptoms, and physical function in individuals with FM.

Search strategy

We searched MEDLINE, EMBASE, CINAHL, SportDiscus, PubMed, PEDro, and the Cochrane Central Register for Controlled Trials (CENTRAL, Issue 3, 2005) up to and including July 2005. We also reviewed reference lists from reviews and meta-analyses of treatment studies.

Selection criteria

Randomized trials that were selected focused on cardiorespiratory endurance, muscle strength and/or flexibility as treatment for FM.

Data collection and analysis

Two of four reviewers independently extracted data for each study. All discrepancies were rechecked and consensus was achieved by discussion. Methodological quality was assessed by two instruments: the van Tulder and the Jadad methodological quality criteria. We used the American College of Sport Medicine (ACSM) guidelines to evaluate whether interventions had provided a training stimulus that would effect changes in physical fitness. Due to significant clinical heterogeneity among the studies we were only able to meta-analyze six aerobic-only studies and two strength-only studies.

Main results

There were a total of 2276 subjects across the 34 included studies; 1264 subjects were assigned to exercise interventions. The 34 studies comprised 47 interventions that included exercise. Effects of several disparate interventions on global well-being, selected FM signs and symptoms, and physical function in individuals with FM were summarized using standardized mean differences (SMD). There is moderate quality evidence that aerobic-only exercise training at recommended intensity levels has positive effects global well-being (SMD 0.49, 95% CI: 0.23 to 0.75) and physical function (SMD 0.66, 95% CI: 0.41 to 0.92) and possibly on pain (SMD 0.65, 95% CI: -0.09 to 1.39) and tender points (SMD 0.23, 95% CI: -0.18 to 0.65). Strength and flexibility remain under-evaluated.

Authors' conclusions

There is 'gold' level evidence (www.cochranemsk.org) that supervised aerobic exercise training has beneficial effects on physical capacity and FM symptoms. Strength training may also have benefits on some FM symptoms. Further studies on muscle strengthening and flexibility are needed. Research on the long-term benefit of exercise for FM is needed.

PLAIN LANGUAGE SUMMARY

Exercise for fibromyalgia

This summary of a Cochrane review presents what we know from research about the effect of exercise for fibromyalgia. The review shows that in people with fibromyalgia:

- moderate intensity aerobic training for 12 weeks may improve overall well-being and physical function; moderate intensity aerobic exercise probably leads to little or no difference in pain or tender points.
- strength training for 12 weeks may result in large reductions in pain, tender points and depression, and large improvement in overall well-being but may not lead to any difference in physical function.
- the exercise programs that were studied were safe for most. The intensity of aerobic exercise training should be increased slowly aiming for a moderate level. If exercisers experience increased symptoms, they should cut back until symptoms improve. If in doubt about adverse effects, they should check with a health care professional.
- it is not known whether exercise training for more than 12 weeks improves other symptoms such as fatigue, stiffness or poor sleep. Many people with FM do have difficulty staying on an exercise program. Strategies to help individuals exercise regularly were not measured in these studies.
- it is not known whether flexibility training, programs combining types of exercise, and programs combining exercise with non-exercise strategies improve the symptoms of fibromyalgia.

What is fibromyalgia and what are the different types of exercise?

Fibromyalgia is a syndrome of persistent widespread pain and tenderness. Individuals may also experience a wide range of other symptoms such as difficulty sleeping, fatigue, stiffness, and depression. Symptoms may put people off exercising but studies show that the majority are able to exercise. Exercise training can include aerobics such as stepping and walking; strengthening exercises such as lifting weights or using resistance machines; and stretching for flexibility. Although exercise is part of the overall management of fibromyalgia, this review examined the effects of exercise when used separately or combined with other strategies such as education programs, biofeedback and medications.

Best estimate of what happens to people with fibromyalgia who take part in aerobic exercise:

In the studies, aerobic exercises were done for at least 20 minutes once a day (or twice for at least 10 minutes), 2 to 3 days a week. Strength training was done 2 to 3 times a week and with at least 8 to 12 repetitions per exercise. The exercise programs lasted between 2 ½ to 24 weeks.

Duloxetine for treating painful neuropathy or chronic pain (Review)

Lunn MPT, Hughes RAC, Wiffen PJ



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[Intervention Review]

Duloxetine for treating painful neuropathy or chronic pain

Michael PT Lunn¹, Richard AC Hughes², Philip J Wiffen³

¹Department of Neurology, National Hospital for Neurology and Neurosurgery, London, UK. ²MRC Centre for Neuromuscular Disease, National Hospital for Neurology and Neurosurgery, London, UK. ³UK Cochrane Centre, Oxford, UK

Contact address: Michael PT Lunn, Department of Neurology, National Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG, UK. michael.lunn@uclh.nhs.uk.

Editorial group: Cochrane Neuromuscular Disease Group.

Publication status and date: Edited (no change to conclusions), published in Issue 4, 2011.

Review content assessed as up-to-date: 1 March 2009.

Citation: Lunn MPT, Hughes RAC, Wiffen PJ. Duloxetine for treating painful neuropathy or chronic pain. *Cochrane Database of Systematic Reviews* 2009, Issue 4. Art. No.: CD007115. DOI: 10.1002/14651858.CD007115.pub2.

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ABSTRACT

Background

Duloxetine is a balanced serotonin and noradrenaline reuptake inhibitor licensed for the treatment of major depressive disorders, urinary stress incontinence and the management of neuropathic pain associated with diabetic peripheral neuropathy. A number of trials have been conducted to investigate the use of duloxetine in neuropathic and nociceptive painful conditions.

Objectives

To assess the benefits and harms of duloxetine for treating painful neuropathy and different types of chronic pain.

Search strategy

We searched The Cochrane Neuromuscular Group Specialized Register (10 March 2009), The Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 3, 2009), MEDLINE (January 1966 to March 2009), EMBASE (January 1980 to March 2009), and www.clinicaltrials.gov to March 2009 and the reference lists of identified publications for trials of duloxetine used for the treatment of painful peripheral neuropathy or chronic pain.

Selection criteria

We selected all randomised or quasi-randomised trials of any formulation of duloxetine, used for the treatment of painful peripheral neuropathy or chronic pain in adult participants.

Data collection and analysis

Two authors extracted data independently onto a specially designed proforma and cross checked them.

Main results

Six trials were identified including 2220 participants. Three studies included participants with painful diabetic neuropathy and three treated participants with fibromyalgia. Duloxetine at 60 mg daily is effective in treating painful diabetic peripheral neuropathy in the short-term to 12 weeks with a risk ratio (RR) for 50% pain reduction at 12 weeks of 1.65 (95% confidence interval (CI) 1.34 to 2.03), number needed to treat (NNT) 6 (95% CI 5 to 10). Duloxetine at 60 mg daily is also effective in fibromyalgia over 12 weeks (RR 50% reduction in pain 1.57, 95% CI 1.20 to 2.06; NNT 8, 95% CI 5 to 17) and 28 weeks (RR 1.58, 95% CI 1.10 to 2.27). Adverse events were common in both treatment and placebo arms but more common in the treatment arm with a dose dependent effect. Most side effects were minor, but 16% of participants stopped the drug due to side effects. Serious adverse events were rare.

Authors' conclusions

There is moderately strong evidence that duloxetine 60 mg and 120 mg daily are efficacious for treating pain in diabetic peripheral neuropathy and fibromyalgia but 20 mg daily is not. Minor side effects are common at therapeutic doses but serious side effects are rare. Direct comparisons of duloxetine with other antidepressants and with other drugs already shown to be efficacious in neuropathic pain would be appropriate and should include unbiased economic analyses.

PLAIN LANGUAGE SUMMARY

Duloxetine for neuropathic pain

Duloxetine is a drug used to treat depression and incontinence and it can be also be useful in treating certain types of pain. Pain can be produced spontaneously from damaged parts of the nervous system used to transmit pain information to the brain (neuropathic pain). When this damage is to nerves outside the spinal cord it is called a neuropathy. Pain is also produced when the nerves sense damage to another tissue (for example a pin being pressed into the skin) and this is called nociceptive pain. Some pain is of unclear origin, as no damage to the nervous system or to the tissues to which the nerves connect can be identified. This sort of pain happens, for example, in fibromyalgia. Duloxetine is also used to treat depression and problems with bladder function but the objective of this review was to consider all the evidence from double-blind randomised controlled trials relating to the use of duloxetine to treat painful neuropathy and chronic pains of all sorts.

We looked at all the published scientific literature and identified six drug trials involving a total of 2220 participants that were of sufficient quality and reliability to include. Three tested the effect of duloxetine on painful diabetic neuropathy and three on the pain of fibromyalgia.

The usual dose of duloxetine is 60 mg. At this dose, there was moderately strong evidence that duloxetine reduced pain in both painful diabetic peripheral neuropathy and fibromyalgia. In diabetic peripheral neuropathic pain the relative rate of 50% improvement with duloxetine 60 mg per day was just over one and a half times more than with placebo. This equates to needing to treat 6 people with diabetic peripheral neuropathic pain with duloxetine to achieve a 50% response in one person. The effect on fibromyalgia was similar. A dose of 20 mg was not effective and a higher dose of 120 mg was no more effective than 60 mg.

Most people taking duloxetine will have at least one side effect. These are mostly minor and are commonly feeling sick, being too awake or too sleepy, developing a headache, having a dry mouth or becoming constipated or dizzy. About one in six people stop duloxetine because of side effects but serious problems caused by duloxetine are very rare.

Duloxetine may be about as good at reducing these sorts of pain as some of the other antidepressant drugs on the market but the evidence supporting this comparison is not strong.

We have concluded that duloxetine is useful for treating pain caused by fibromyalgia and diabetic neuropathy and it seems to be about as effective as other similar drugs already on the market. No direct comparison has been performed between duloxetine and any of these other drugs. As yet it is not clear whether the use of duloxetine is cost effective when compared to the other drugs already in use.

Milnacipran for neuropathic pain and fibromyalgia in adults (Review)

Derry S, Gill D, Phillips T, Moore RA



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[Intervention Review]

Milnacipran for neuropathic pain and fibromyalgia in adults

Sheena Derry¹, Dipender Gill¹, Tudor Phillips¹, R Andrew Moore¹

¹Pain Research and Nuffield Department of Clinical Neurosciences (Nuffield Division of Anaesthetics), University of Oxford, Oxford, UK

Contact address: Sheena Derry, Pain Research and Nuffield Department of Clinical Neurosciences (Nuffield Division of Anaesthetics), University of Oxford, Churchill Hospital, Oxford, Oxfordshire, OX3 7LE, UK. sheena.derry@pru.ox.ac.uk.

Editorial group: Cochrane Pain, Palliative and Supportive Care Group.

Publication status and date: New, published in Issue 3, 2012.

Review content assessed as up-to-date: 4 January 2012.

Citation: Derry S, Gill D, Phillips T, Moore RA. Milnacipran for neuropathic pain and fibromyalgia in adults. *Cochrane Database of Systematic Reviews* 2012, Issue 3. Art. No.: CD008244. DOI: 10.1002/14651858.CD008244.pub2.

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ABSTRACT

Background

Milnacipran is a [serotonin-norepinephrine reuptake inhibitor](#) (SNRI) that is sometimes used to treat chronic neuropathic pain and fibromyalgia.

Objectives

To evaluate the analgesic efficacy and adverse effects of milnacipran in the management of chronic neuropathic pain or fibromyalgia.

Search methods

We searched CENTRAL, MEDLINE, and EMBASE to 4th of January 2012, together with reference lists of retrieved papers and reviews.

Selection criteria

We included randomised, double-blind studies of eight weeks duration or longer, comparing milnacipran with placebo or another active treatment in chronic neuropathic pain or fibromyalgia.

Data collection and analysis

We extracted efficacy and adverse event data, and two study authors examined issues of study quality independently.

Main results

Five studies (4138 participants) were included, all of which were placebo-controlled, involved participants with fibromyalgia, and used titration to a target dose of 100 mg or 200 mg milnacipran. There were no other active comparators or studies in other neuropathic pain conditions. Study quality was generally good, although the imputation method used in analyses of the primary outcomes could overestimate treatment effect.

Both doses of milnacipran provided moderate levels of pain relief to about 40% of those treated, compared to 30% with placebo, giving a number needed to treat of 8 to 10. Adverse events were common in both milnacipran (87%) and placebo (78%) groups, but serious adverse events (< 2%) did not differ between groups. Nausea and constipation were the most common events showing the greatest difference between groups (number needed to treat for an additional harmful outcome of 7 and 13 respectively, compared with placebo).

Withdrawals for any reason were more common with milnacipran than placebo, and more common with 200 mg than 100 mg (NNH of 23 and 8.8 respectively, compared with placebo). This was largely driven by adverse event withdrawals, where the NNH compared with placebo was 14 for 100 mg, and 7.0 for 200 mg. Withdrawals due to lack of efficacy were more common with milnacipran than placebo but did not differ between doses (number needed to treat to prevent an additional unwanted outcome of 45 and 41 respectively).

Authors' conclusions

The evidence available indicates that milnacipran 100 mg or 200 mg is effective for a minority in the treatment of pain due to fibromyalgia, providing moderate levels of pain relief (at least 30%) to about 40% of participants, compared with about 30% with placebo. There were insufficient data to assess substantial levels of pain relief (at least 50%), and the use of last observation carried forward imputation may overestimate drug efficacy. Milnacipran is associated with increased adverse events and adverse event withdrawals, which were significantly greater for the higher dose. There were no data for the use of milnacipran for other chronic neuropathic pain conditions.

PLAIN LANGUAGE SUMMARY

Milnacipran for chronic neuropathic pain and fibromyalgia in adults

The aim of this review was to assess how effective milnacipran is for treating chronic neuropathic pain or fibromyalgia. We identified no studies using milnacipran in neuropathic pain, but five studies in fibromyalgia satisfied the inclusion criteria. Fibromyalgia is a complex pain syndrome, defined as widespread pain for longer than three months; the original diagnostic criteria involved pain on palpation at 11 or more of a number of specified tender points (Wolfe 1990), with later criteria including both widespread pain and symptom severity (Wolfe 2010). The studies included over 4000 participants treated with milnacipran 100 mg or 200 mg, or placebo, for eight to 24 weeks at the target dose. Overall study quality was good, although the method of analysis for our primary outcomes could overestimate treatment effect.

Milnacipran at either dose provided moderate pain relief (at least 30% reduction in pain intensity) to 10% more participants than did placebo. This relatively modest effect may be clinically important in this difficult to treat condition. Adverse events were reported by the majority of participants in all groups, but were more common with milnacipran than placebo, with nausea and constipation showing the greatest differences. Serious adverse events were uncommon (less than 2%) and did not differ between treatment groups. Withdrawals due to adverse events were also more common with milnacipran than placebo, and were more common with 200 mg than 100 mg, while withdrawals due to lack of efficacy were less common with milnacipran, with no difference between doses.

Milnacipran has shown modest effects in a minority of participants with fibromyalgia, and several technical issues indicate that even this modest effect may overstate effectiveness in clinical practice. The drug may be a useful option if first-line treatments fail.

BACKGROUND

Description of the condition

Neuropathic pain, unlike nociceptive pain such as gout and other forms of arthritis, is caused by nerve damage, often accompanied by changes in the central nervous system (CNS). The new (2011) definition of neuropathic pain is "pain caused by a lesion or disease of the somatosensory system" (Jensen 2011). Fibromyalgia is a complex pain syndrome, defined as widespread pain for longer than three months with pain on palpation at 11 or more of 18

specified tender points (Wolfe 1990), and frequently associated with other symptoms such as poor sleep, fatigue, and depression. More recently, a definition of fibromyalgia has been proposed based on symptom severity and the presence of widespread pain (Wolfe 2010). The cause or causes of fibromyalgia are not well understood, but it has features in common with neuropathic pain, including changes in the CNS. Many people with these conditions are significantly disabled with moderate or severe pain for many years. Conventional analgesics are usually not effective, although opioids may be in some individuals. Others may derive

Botulinum toxin for myofascial pain syndromes in adults (Review)

Soares A, Andriolo RB, Atallah ÁN, da Silva EMK, da Silva EMK



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Botulinum toxin for myofascial pain syndromes in adults (Review)

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Botulinum toxin for myofascial pain syndromes in adults

Adriana Soares¹, Régis B Andriolo², Álvaro N Atallah³, Edina MK da Silva⁴, Edina MK da Silva⁵

¹Department of Medicine, Universidade Federal de São Paulo, Belo Horizonte, Brazil. ²Department of Public Health, Universidade do Estado do Pará, Belém, Brazil. ³Brazilian Cochrane Centre, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil. ⁴Emergency Medicine and Evidence Based Medicine, Brazilian Cochrane Centre, Universidade Federal de São Paulo, São Paulo, Brazil. ⁵Emergency Medicine and Evidence Based Medicine, Universidade Federal de São Paulo, São Paulo, Brazil

Contact address: Adriana Soares, Department of Medicine, Universidade Federal de São Paulo, Rua Curral Del Rey, 389 apt.104 Bairro Padre Eustaquio, Belo Horizonte, Minas Gerais, 30720-220, Brazil. adrianapacossoares@hotmail.com.

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ABSTRACT

Background

Myofascial pain syndrome (MPS) is a regional muscular pain syndrome characterised by the presence of trigger points, which are painful points in one or more muscles. The pain can be felt at the site where the trigger point is located or it can be felt away from that place when the muscle is pressed (referred pain). Botulinum toxin is a protein produced by the bacterium *Clostridium botulinum* and is a potent neurotoxin that eventually inhibits muscle contractions. It is capable of selectively weakening painful muscles and interrupting the pain cycle.

Objectives

To assess the effectiveness and safety of botulinum toxin in treating MPS, excluding MPS in neck and head muscles.

Search methods

The search strategy was composed of terms for myofascial pain and botulinum toxin. We searched the Cochrane Pain, Palliative and Supportive Care (PaPaS) Review Group's Specialised Register until December 2011, CENTRAL (Cochrane Database of Systematic Reviews 2011, Issue 4), PUBMED (from 1966 to 2011), EMBASE (from 1980 to 2011) and LILACS (from 1982 to 2011). There was no language restriction.

Selection criteria

We included randomised controlled trials (RCTs) involving botulinum toxin for treating participants with MPS. We excluded studies with MPS of the neck and head from this review, as they have already been assessed in existing systematic reviews. We considered a diagnosis of MPS to be based on the identification of trigger points in the taut band through palpation of sensitive nodules, local twitch response and specific patterns of referred pain associated with each trigger point.

Data collection and analysis

Two review authors independently screened identified studies, extracted data, assessed trial quality and analysed results using the Cochrane PaPaS Review Group criteria.

Main results

Four studies with a total of 233 participants, comparing botulinum toxin A (BTXA) with placebo, met the inclusion criteria. In one study with 145 participants, a significant improvement rate of pain intensity scores, as shown by the mean difference (MD) of -0.23 (95% confidence interval (CI) -0.26 to -0.20; P value < 0.00001) and duration of daily pain (MD -1.11; 95% CI -1.37 to -0.85; P value < 0.00001), was demonstrated when comparing BTXA with placebo. The three other studies showed that there was no statistically significant difference between BTXA and placebo in pain intensity.

Authors' conclusions

There is inconclusive evidence to support the use of botulinum toxin in the treatment of MPS based on data from four studies with a total of 233 participants, which we considered adequate to be included in this review. Meta-analyses were not possible due to the heterogeneity between studies. We suggest that in future studies the same methodology to assess pain, a standardised dose of treatment, follow-up of at least four months (to observe the maximum/minimum curve of the drug effect) and appropriate data presentation should be used. More high-quality RCTs of botulinum toxin for treating MPS need to be conducted before firm conclusions on its effectiveness and safety can be drawn.

PLAIN LANGUAGE SUMMARY

Botulinum toxin injectable drug for myofascial pain syndromes (a painful condition that could affect any muscle in the body) in adults

Myofascial pain syndrome (MPS) is a regional muscular pain syndrome characterised by the presence of trigger points (painful points) in one or more muscles. The pain can be at the trigger point site or it can be felt away from it when the muscle is pressed, which is called referred pain. Botulinum toxin is a potent chemical that blocks the communication between nerves and muscles and inhibits muscle contractions where the trigger points are located, which may result in pain relief in the area it is injected. The purpose of this review is to assess how effective botulinum toxin is at reducing pain in patients with MPS. We identified four studies with 233 participants, comparing botulinum toxin A with placebo (control group). There is inconclusive evidence to support the use of botulinum toxin in the treatment of MPS. More high-quality randomised controlled trials of botulinum toxin for treating MPS need to be conducted before firm conclusions on its effectiveness and safety can be drawn.

BACKGROUND

Description of the condition

Myofascial pain syndrome (MPS) is characterised by acute or chronic regional muscle pain associated with single or multiple restricted painful regions (trigger points) within taut muscle bands. It is also associated with stiffness and local twitch response when stimulated by digital pressure or during located needling generating local or referred pain (Ernberg 2002; Gerwin 1995; Guststein 1938; Simons 1976; Simons 1999; Sola 1955).

Individuals who have regional pain present with a high prevalence of MPS. Studies carried out in pain management centres and clinics of different specialties have shown prevalence ranging from 30% to 93% (mean 6 in 10) in participants complaining of regionalised pain (Fishbain 1986; Friction 1985; Gerwin 1995;

Han 1997; Schiffman 1990; Skootsky 1989), in 30 to 50-year-olds (Simons 1999), and in women (Han 1997; Sola 1955).

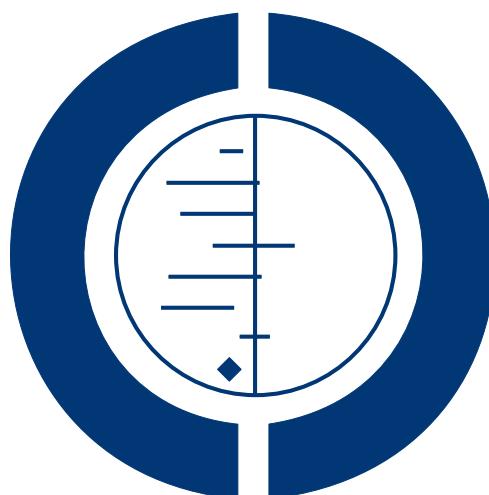
The trapezius, levator scapula, infraspinatus and scalenes muscles of the upper body are the areas most frequently affected by MPS (Sola 1955). A number of causal factors associated with MPS have been suggested such as: acute physical overload, deep pain impulse, emotional tension, postural habits, fatigue, hypovitaminosis, infections, physical inactivity, poor physical conditioning, repetitive musculoskeletal micro traumas and trauma (Edwards 2005; Friction 1985; Friction 1994; Laskin 1969; Simons 1976; Simons 1999).

The diagnosis of MPS is based on the identification of trigger points in the taut band through palpation of sensitive nodules, local twitch response and specific patterns of pain referral associated with each trigger point (Friction 1985; Simons 1999).

MPS treatment can be multi-dimensional and consists of trig-

Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome (Review)

Tort S, Urrútia G, Nishishinya MB, Walitt B



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[Intervention Review]

Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome

Sera Tort¹, Gerard Urrútia², María Betina Nishishinya¹, Brian Walitt³

¹Iberoamerican Cochrane Centre, Institute of Biomedical Research (IIB Sant Pau), Barcelona, Spain. ²Iberoamerican Cochrane Centre - IIB Sant Pau, CIBER Epidemiología y Salud Pública (CIBERESP), Spain, Barcelona, Spain. ³Georgetown University Medical Center, Washington Hospital Center, Washington, DC, USA

Contact address: Sera Tort, Iberoamerican Cochrane Centre, Institute of Biomedical Research (IIB Sant Pau), Sant Antoni Maria Claret 171, Edifici Casa de Convalescència, Barcelona, Catalonia, 08041, Spain. sera.tort@cochrane.es. seratort@terra.es.

Editorial group: Cochrane Musculoskeletal Group.

Publication status and date: New, published in Issue 4, 2012.

Review content assessed as up-to-date: 25 January 2011.

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ABSTRACT

Background

Fibromyalgia (FM) syndrome is a chronic condition of unknown aetiology characterised by musculoskeletal pain that often co-exists with sleep disturbance, cognitive dysfunction and fatigue. Patients often report high disability levels and poor quality of life. Since there is no specific treatment that alters the pathogenesis of FM, drug therapy focuses on pain reduction and improvement of other bothersome symptoms.

Objectives

The objective of this review was to assess the effectiveness and safety of monoamine oxidase inhibitors (MAOIs) in the treatment of FM syndrome.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 10), MEDLINE (1966 to November 2010), EMBASE (1980 to November 2010) and the reference lists of reviewed articles.

Selection criteria

We selected all randomised, double-blind trials of MAOIs used for the treatment of FM pain in adult participants.

Data collection and analysis

Two authors assessed risk of bias and extracted data independently onto a specially designed pro forma and a third review author cross-checked them.

Main results

We included two studies of inconsistent risk of bias with a total of 230 patients diagnosed with FM. We evaluated two MAOIs: pirlindole and moclobemide. Pirlindole showed statistically significant results compared with placebo for several outcomes (pain, tender points and overall assessment by the patient and the physician), whereas moclobemide did not show statistically significant differences between groups. Pooled results of the two studies displayed a modest effect size in pain (mean difference (MD) -1.45 (121 patients;

95% confidence interval (CI) -2.71 to -0.20; number needed to treat (NNT) 2 (95% CI 1 to 12); $I^2 = 59\%$), implying a minimal clinically important difference (MCID) and a small effect on tender points (standardised mean difference (SMD) -0.36 (121 patients; 95% CI -0.72 to -0.00; $I^2 = 31\%$)). No effect was seen on global assessment by patient. Physical function and sleep disturbance were not measured. The most frequent adverse events were nausea and vomiting, with statistically significant differences between groups (risk ratio (RR) 7.82 (89 patients; 95% CI 1.02 to 59.97; NNT 7 (95% CI 4 to 33))).

Authors' conclusions

Data suggest that the effectiveness of MAOIs for the treatment of FM symptoms is limited. Although we observed a moderate effect size on pain and a small one on tender points, these results should be taken with caution as they are only based on two studies with a small number of patients and inconsistent risk of bias among them.

PLAIN LANGUAGE SUMMARY

Monoamine oxidase inhibitors (MAOIs) for fibromyalgia

This summary of a Cochrane review presents what we know from research about the effect of MAOIs for fibromyalgia (FM).

The review shows that in people with FM:

MAOIs may slightly improve pain and tender points in the short term compared to placebo. Of the MAOIs studied, pirlindole seems more effective than moclobemide.

We often do not have precise information about side effects and complications. This is particularly true for rare but serious side effects. The most frequent side effects seen in the studies included nausea and vomiting. However, MAOIs are known to have serious and potentially fatal interactions with a variety of foods and other medications.

What is fibromyalgia and what are MAOIs?

Fibromyalgia is a chronic condition characterised by generalised pains along with other problems such as sleep disturbances, fatigue and cognitive dysfunction. MAOIs are a certain type of antidepressants that are occasionally used to treat fibromyalgia symptoms. Other antidepressants such as tricyclic agents have demonstrated that they can help to relieve pain, tender points, fatigue and sleep disturbances in people with fibromyalgia, but there is a need to know if MAOIs might also help.

Best estimate of what happens to people with fibromyalgia who take MAOIs:

Pain (higher scores mean worse or more severe pain)

- People who took MAOIs rated their pain to be 1.45 points lower on a scale of 0 to 10 compared to people who took placebo.

Global assessment (by patient)

- People who took MAOIs showed no difference in their global assessment compared to people who took placebo.

Tender points

- People who took MAOIs had a lower tender point score and a lower number of tender points (-0.36 difference) than people who took placebo after four weeks.

Physical function

- No information about physical function was provided.

Sleep disturbance

- No information about sleep disturbance was provided.

Adverse events (nausea and vomiting)

- 16 more people out of 100 who took MAOIs (pirlindole) had nausea and vomiting.

- 18 people out of 100 who took MAOIs (pirlindole) had nausea and vomiting.

- 2 people out of 100 who took placebo had nausea and vomiting.

- No information regarding people who took moclobemide is available.

Amitriptyline for neuropathic pain and fibromyalgia in adults (Review)

Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ



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Amitriptyline for neuropathic pain and fibromyalgia in adults (Review)
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Amitriptyline for neuropathic pain and fibromyalgia in adults

R Andrew Moore¹, Sheena Derry¹, Dominic Aldington², Peter Cole³, Philip J Wiffen¹

¹Pain Research and Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK. ²Royal Hampshire County Hospital, Winchester, UK. ³Oxford Pain Relief Unit, Churchill Hospital, Oxford University Hospitals NHS Trust, Oxford, UK

Contact address: R Andrew Moore, Pain Research and Nuffield Department of Clinical Neurosciences, University of Oxford, Pain Research Unit, Churchill Hospital, Oxford, Oxfordshire, OX3 7LE, UK. andrew.moore@ndcn.ox.ac.uk.

Editorial group: Cochrane Pain, Palliative and Supportive Care Group.

Publication status and date: New, published in Issue 12, 2012.

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ABSTRACT

Background

Amitriptyline is a tricyclic antidepressant that is widely used to treat chronic neuropathic pain (pain due to nerve damage) and fibromyalgia, and is recommended in many guidelines. These types of pain can be treated with antidepressant drugs in doses below those at which the drugs act as antidepressants.

Objectives

To assess the analgesic efficacy of amitriptyline for chronic neuropathic pain and fibromyalgia. To assess the adverse events associated with the clinical use of amitriptyline for chronic neuropathic pain and fibromyalgia.

Search methods

We searched CENTRAL, MEDLINE, and EMBASE to September 2012, together with reference lists of retrieved papers, previous systematic reviews, and other reviews; we also used our own handsearched database for older studies.

Selection criteria

We included randomised, double-blind studies of at least four weeks' duration comparing amitriptyline with placebo or another active treatment in chronic neuropathic pain or fibromyalgia.

Data collection and analysis

We extracted efficacy and adverse event data, and two study authors examined issues of study quality independently. We performed analysis using two tiers of evidence. The first tier used data meeting current best standards, where studies reported the outcome of at least 50% pain intensity reduction over baseline (or its equivalent), without the use of last observation carried forward (LOCF) or other imputation method for dropouts, reported an intention-to-treat (ITT) analysis, lasted 8 to 12 weeks or longer, had a parallel-group design, and where there were at least 200 participants in the comparison. The second tier used data that failed to meet this standard and were therefore subject to potential bias.

Main results

Twenty-one studies (1437 participants) were included; they individually involved between 15 and 235 participants, only four involved over 100 participants, and the median study size was 44 participants. The median duration was six weeks. Ten studies had a cross-over design. Doses of amitriptyline were generally between 25 mg and 125 mg, and dose escalation was common.

There was no top-tier evidence for amitriptyline in treating neuropathic pain or fibromyalgia.

Second-tier evidence indicated no evidence of effect in cancer-related neuropathic pain or HIV-related neuropathic pain, but some evidence of effect in painful diabetic neuropathy (PDN), mixed neuropathic pain, and fibromyalgia. Combining the classic neuropathic pain conditions of PDN, postherpetic neuralgia (PHN) and post-stroke pain with fibromyalgia for second-tier evidence, in eight studies and 687 participants, there was a statistically significant benefit (risk ratio (RR) 2.3, 95% confidence interval (CI) 1.8 to 3.1) with a number needed to treat (NNT) of 4.6 (3.6 to 6.6). The analysis showed that even using this potentially biased data, only about 38% of participants benefited with amitriptyline and 16% with placebo; most participants did not get adequate pain relief. Potential benefits of amitriptyline were supported by a lower rate of lack of efficacy withdrawals; 8/153 (5%) withdrew because of lack of efficacy with amitriptyline and 14/119 (12%) with placebo.

More participants experienced at least one adverse event; 64% of participants taking amitriptyline and 40% taking placebo. The RR was 1.5 (95% CI 1.4 to 1.7) and the number needed to treat to harm was 4.1 (95% CI 3.2 to 5.7). Adverse event and all-cause withdrawals were not different.

Authors' conclusions

Amitriptyline has been a first-line treatment for neuropathic pain for many years. The fact that there is no supportive unbiased evidence for a beneficial effect is disappointing, but has to be balanced against decades of successful treatment in many patients with neuropathic pain or fibromyalgia. There is no good evidence of a lack of effect; rather our concern should be of overestimation of treatment effect. Amitriptyline should continue to be used as part of the treatment of neuropathic pain or fibromyalgia, but only a minority of patients will achieve satisfactory pain relief. Limited information suggests that failure with one antidepressant does not mean failure with all.

It is unlikely that any large randomised trials of amitriptyline will be conducted in specific neuropathic pain conditions or in fibromyalgia to prove efficacy.

PLAIN LANGUAGE SUMMARY

Amitriptyline for neuropathic pain and fibromyalgia in adults

The review set out to examine how well amitriptyline worked in treating neuropathic pain or fibromyalgia, where the definition of worked involved both a high level of pain relief and the ability to take the tablets over a longer time without side effects being intolerable. There were no studies that could provide an answer that was trustworthy or reliable, because most studies were relatively old, and used methods or reported results that we now recognise as making benefits seem better than they are. This is disappointing, but we can still make useful comments about the drug.

Amitriptyline probably does not work in neuropathic pain associated with HIV or treatments for cancer. Amitriptyline probably does work in other types of neuropathic pain (painful diabetic neuropathy, postherpetic neuralgia, and post-stroke pain, and in fibromyalgia), though we cannot be certain of this. Our best guess is that amitriptyline provides pain relief in about 1 in 4 (25%) more people than does placebo, and about 1 in 4 (25%) more people than placebo report having at least one adverse event, probably not serious but disconcerting; we cannot trust either figure based on the information available.

The most important message is that amitriptyline probably does give really good pain relief to some patients with neuropathic pain or fibromyalgia, but only a minority of them; amitriptyline will not work for most people.

Clonazepam for neuropathic pain and fibromyalgia in adults (Review)

Corrigan R, Derry S, Wiffen PJ, Moore RA



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Clonazepam for neuropathic pain and fibromyalgia in adults

Ruth Corrigan¹, Sheena Derry², Philip J Wiffen², R Andrew Moore²

¹Pain Research and Nuffield Department of Clinical Neurosciences (Nuffield Division of Anaesthetics), University of Oxford, Oxford, UK. ²Pain Research and Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK

Contact address: Sheena Derry, Pain Research and Nuffield Department of Clinical Neurosciences, University of Oxford, Pain Research Unit, Churchill Hospital, Oxford, Oxfordshire, OX3 7LE, UK. sheena.derry@ndcn.ox.ac.uk.

Editorial group: Cochrane Pain, Palliative and Supportive Care Group.

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Review content assessed as up-to-date: 4 April 2012.

Citation: Corrigan R, Derry S, Wiffen PJ, Moore RA. Clonazepam for neuropathic pain and fibromyalgia in adults. *Cochrane Database of Systematic Reviews* 2012, Issue 5. Art. No.: CD009486. DOI: 10.1002/14651858.CD009486.pub2.

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ABSTRACT

Background

Antiepileptic drugs have been used in pain management since the 1960s; some have shown efficacy in treating different neuropathic pain conditions. Clonazepam, a benzodiazepine, is an established antiepileptic drug, but its place in the treatment of neuropathic pain is unclear.

Objectives

To assess the analgesic efficacy and adverse effects of the antiepileptic drug clonazepam in neuropathic pain and fibromyalgia.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 2), MEDLINE, and EMBASE to 28 February 2012, together with reference lists of retrieved papers and reviews, and ClinicalTrials.gov.

Selection criteria

We planned to include randomised, double-blind studies of eight weeks duration or longer, comparing clonazepam with placebo or another active treatment in chronic neuropathic pain or fibromyalgia.

Data collection and analysis

Two review authors would independently extract data for efficacy and adverse events, and examine issues of study quality.

Main results

We did not identify any studies that satisfied the inclusion criteria.

Authors' conclusions

This review uncovered no evidence of sufficient quality to support the use of clonazepam in chronic neuropathic pain or fibromyalgia.

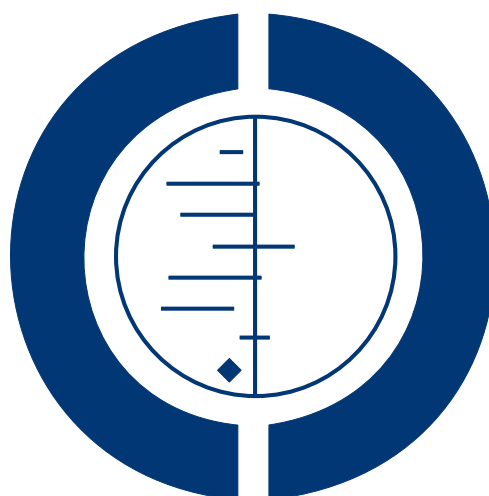
PLAIN LANGUAGE SUMMARY

Clonazepam for neuropathic pain and fibromyalgia in adults

Clonazepam for neuropathic pain and fibromyalgia in adults (Review)
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Phenytoin for neuropathic pain and fibromyalgia in adults (Review)

Birse F, Derry S, Moore RA



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[Intervention Review]

Phenytoin for neuropathic pain and fibromyalgia in adults

Fraser Birse¹, Sheena Derry², R Andrew Moore²

¹Pain Research and Nuffield Department of Clinical Neurosciences (Nuffield Division of Anaesthetics), University of Oxford, Oxford, UK. ²Pain Research and Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK

Contact address: Sheena Derry, Pain Research and Nuffield Department of Clinical Neurosciences, University of Oxford, Pain Research Unit, Churchill Hospital, Oxford, Oxfordshire, OX3 7LE, UK. sheena.derry@ndcn.ox.ac.uk.

Editorial group: Cochrane Pain, Palliative and Supportive Care Group.

Publication status and date: Edited (no change to conclusions), published in Issue 7, 2013.

Review content assessed as up-to-date: 4 April 2012.

Citation: Birse F, Derry S, Moore RA. Phenytoin for neuropathic pain and fibromyalgia in adults. *Cochrane Database of Systematic Reviews* 2012, Issue 5. Art. No.: CD009485. DOI: 10.1002/14651858.CD009485.pub2.

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ABSTRACT

Background

Antiepileptic drugs have been used in pain management since the 1960s; some have shown efficacy in treating different neuropathic pain conditions. Phenytoin is an established antiepileptic drug that has been used occasionally to treat intractable trigeminal neuralgia.

Objectives

To assess the analgesic efficacy and adverse effects of the antiepileptic drug phenytoin in neuropathic pain and fibromyalgia.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 2), MEDLINE, and EMBASE to 28 February 2012, together with reference lists of retrieved papers and reviews, and ClinicalTrials.gov.

Selection criteria

We planned to include randomised, double-blind studies of eight weeks duration or longer, comparing phenytoin with placebo or another active treatment in chronic neuropathic pain or fibromyalgia.

Data collection and analysis

Two review authors would independently extract data for efficacy and adverse events, and examine issues of study quality.

Main results

We did not identify any studies that satisfied the inclusion criteria.

Authors' conclusions

This review uncovered no evidence of sufficient quality to support the use of phenytoin in chronic neuropathic pain or fibromyalgia.

PLAIN LANGUAGE SUMMARY

Phenytoin for neuropathic pain and fibromyalgia in adults

Phenytoin for neuropathic pain and fibromyalgia in adults (Review)

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Acupuncture for treating fibromyalgia (Review)

Deare JC, Zheng Z, Xue CCL, Liu JP, Shang J, Scott SW, Littlejohn G



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Acupuncture for treating fibromyalgia (Review)

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Acupuncture for treating fibromyalgia

John C Deare¹, Zhen Zheng², Charlie CL Xue², Jian Ping Liu³, Jingsheng Shang⁴, Sean W Scott⁵, Geoff Littlejohn⁶

¹Compmed Health Institute, Southport, Queensland, Australia; and Traditional & Complementary Medicine Program, Health Innovations Research Institute, Discipline of Chinese Medicine, School of Health Sciences, RMIT University, Bundoora, Australia. ²Traditional & Complementary Medicine Research Program, Health Innovations Research Institute and Discipline of Chinese Medicine, School of Health Sciences, RMIT University, Bundoora, Australia. ³Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, China. ⁴Akupunktoren Bruno Aamo AS, Tromsø, Norway. ⁵Department of Emergency Medicine, Royal North Shore Hospital, St Leonards, Australia. ⁶Department of Rheumatology, Monash Medical Centre, Clayton, Australia

Contact address: Zhen Zheng, Traditional & Complementary Medicine Research Program, Health Innovations Research Institute and Discipline of Chinese Medicine, School of Health Sciences, RMIT University, PO Box 71, Bundoora, Victoria, 3083, Australia. zhen.zheng@rmit.edu.au.

Editorial group: Cochrane Musculoskeletal Group.

Publication status and date: New, published in Issue 5, 2013.

Review content assessed as up-to-date: 15 January 2012.

Citation: Deare JC, Zheng Z, Xue CCL, Liu JP, Shang J, Scott SW, Littlejohn G. Acupuncture for treating fibromyalgia. *Cochrane Database of Systematic Reviews* 2013, Issue 5. Art. No.: CD007070. DOI: 10.1002/14651858.CD007070.pub2.

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ABSTRACT

Background

One in five fibromyalgia sufferers use acupuncture treatment within two years of diagnosis.

Objectives

To examine the benefits and safety of acupuncture treatment for fibromyalgia.

Search methods

We searched CENTRAL, PubMed, EMBASE, CINAHL, National Research Register, HSR Project and Current Contents, as well as the Chinese databases VIP and Wangfang to January 2012 with no language restrictions.

Selection criteria

Randomised and quasi-randomised studies evaluating any type of invasive acupuncture for fibromyalgia diagnosed according to the American College of Rheumatology (ACR) criteria, and reporting any main outcome: pain, physical function, fatigue, sleep, total well-being, stiffness and adverse events.

Data collection and analysis

Two author pairs selected trials, extracted data and assessed risk of bias. Treatment effects were reported as standardised mean differences (SMD) and 95% confidence intervals (CI) for continuous outcomes using different measurement tools (pain, physical function, fatigue, sleep, total well-being and stiffness) and risk ratio (RR) and 95% CI for dichotomous outcomes (adverse events). We pooled data using the random-effects model.

Main results

Nine trials (395 participants) were included. All studies except one were at low risk of selection bias; five were at risk of selective reporting bias (favouring either treatment group); two were subject to attrition bias (favouring acupuncture); three were subject to performance bias (favouring acupuncture) and one to detection bias (favouring acupuncture). Three studies utilised electro-acupuncture (EA) with the remainder using manual acupuncture (MA) without electrical stimulation. All studies used 'formula acupuncture' except for one, which used trigger points.

Low quality evidence from one study (13 participants) showed EA improved symptoms with no adverse events at one month following treatment. Mean pain in the non-treatment control group was 70 points on a 100 point scale; EA reduced pain by a mean of 22 points (95% confidence interval (CI) 4 to 41), or 22% absolute improvement. Control group global well-being was 66.5 points on a 100 point scale; EA improved well-being by a mean of 15 points (95% CI 5 to 26 points). Control group stiffness was 4.8 points on a 0 to 10 point; EA reduced stiffness by a mean of 0.9 points (95% CI 0.1 to 2 points; absolute reduction 9%, 95% CI 4% to 16%). Fatigue was 4.5 points (10 point scale) without treatment; EA reduced fatigue by a mean of 1 point (95% CI 0.22 to 2 points), absolute reduction 11% (2% to 20%). There was no difference in sleep quality (MD 0.4 points, 95% CI -1 to 0.21 points, 10 point scale), and physical function was not reported.

Moderate quality evidence from six studies (286 participants) indicated that acupuncture (EA or MA) was no better than sham acupuncture, except for less stiffness at one month. Subgroup analysis of two studies (104 participants) indicated benefits of EA. Mean pain was 70 points on 0 to 100 point scale with sham treatment; EA reduced pain by 13% (5% to 22%); (SMD -0.63, 95% CI -1.02 to -0.23). Global well-being was 5.2 points on a 10 point scale with sham treatment; EA improved well-being; SMD 0.65, 95% CI 0.26 to 1.05; absolute improvement 11% (4% to 17%). EA improved sleep, from 3 points on a 0 to 10 point scale in the sham group; SMD 0.40 (95% CI 0.01 to 0.79); absolute improvement 8% (0.2% to 16%). Low-quality evidence from one study suggested that MA group resulted in poorer physical function: mean function in the sham group was 28 points (100 point scale); treatment worsened function by a mean of 6 points (95% CI -10.9 to -0.7). Low-quality evidence from three trials (289 participants) suggested no difference in adverse events between real (9%) and sham acupuncture (35%); RR 0.44 (95% CI 0.12 to 1.63).

Moderate quality evidence from one study (58 participants) found that compared with standard therapy alone (antidepressants and exercise), adjunct acupuncture therapy reduced pain at one month after treatment: mean pain was 8 points on a 0 to 10 point scale in the standard therapy group; treatment reduced pain by 3 points (95% CI -3.9 to -2.1), an absolute reduction of 30% (21% to 39%). Two people treated with acupuncture reported adverse events; there were none in the control group (RR 3.57; 95% CI 0.18 to 71.21). Global well-being, sleep, fatigue and stiffness were not reported. Physical function data were not usable.

Low quality evidence from one study (38 participants) showed a short-term benefit of acupuncture over antidepressants in pain relief: mean pain was 29 points (0 to 100 point scale) in the antidepressant group; acupuncture reduced pain by 17 points (95% CI -24.1 to -10.5). Other outcomes or adverse events were not reported.

Moderate-quality evidence from one study (41 participants) indicated that deep needling with or without *deqi* did not differ in pain, fatigue, function or adverse events. Other outcomes were not reported.

Four studies reported no differences between acupuncture and control or other treatments described at six to seven months follow-up.

No serious adverse events were reported, but there were insufficient adverse events to be certain of the risks.

Authors' conclusions

There is low to moderate-level evidence that compared with no treatment and standard therapy, acupuncture improves pain and stiffness in people with fibromyalgia. There is moderate-level evidence that the effect of acupuncture does not differ from sham acupuncture in reducing pain or fatigue, or improving sleep or global well-being. EA is probably better than MA for pain and stiffness reduction and improvement of global well-being, sleep and fatigue. The effect lasts up to one month, but is not maintained at six months follow-up. MA probably does not improve pain or physical functioning. Acupuncture appears safe. People with fibromyalgia may consider using EA alone or with exercise and medication. The small sample size, scarcity of studies for each comparison, lack of an ideal sham acupuncture weaken the level of evidence and its clinical implications. Larger studies are warranted.

PLAIN LANGUAGE SUMMARY

Acupuncture for fibromyalgia

Acupuncture for treating fibromyalgia (Review)

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Original article

Evidence for the efficacy of complementary and alternative medicines in the management of fibromyalgia: a systematic review

Vijitha De Silva^{1,2}, Ashraf El-Metwally¹, Edzard Ernst³, George Lewith⁴ and Gary J. Macfarlane¹, on behalf of the Arthritis Research Campaign working group on complementary and alternative medicines*

Abstract

Objective. To critically evaluate the evidence regarding complementary and alternative medicines (CAMs) taken orally or applied topically for the treatment of FM.

Methods. Randomized controlled trials of FM using CAMs, in comparison with other treatments or placebo, published in English up to March 2009, were eligible for inclusion. They were identified using systematic searches of bibliographic databases and manual searching of reference lists. Information was extracted on outcomes, and statistical significance, in comparison with alternative treatment or placebo, and side effects were reported. The methodological quality of the primary studies was determined.

Results. Single studies on four CAMs, and three on different approaches to homeopathic care were identified. Their methodological quality was moderate. The homeopathy studies were small, but each reported an improvement in pain. The effects of anthocyanidins, capsaicin and S-adenosylmethionine each showed at least one statistically significant improved outcome compared with placebo. However, the studies of anthocyanidins and capsaicin only demonstrated an improvement in a single outcome, sleep disturbance and tenderness, respectively, of several outcomes considered. No evidence of efficacy was found regarding Soy in a single study. Most of these CAMs were free of major adverse effects and usually associated with only minor adverse effects such as dizziness, nausea and stomach upsets.

Conclusion. There is insufficient evidence on any CAM, taken orally or applied topically, for FM. The small number of positive studies lack replication. Further high-quality trials are necessary to determine whether these initial findings can be supported by a larger evidence base.

Key words: Fibromyalgia, Complementary and alternative medicine, Anthocyanidins, Capsaicin, Soy, S-adenosylmethionine, Homeopathy.

¹Aberdeen Pain Research Collaboration (Epidemiology Group), School of Medicine and Dentistry, University of Aberdeen, Aberdeen, UK,
²Department of Community Medicine, University of Ruhuna, Sri Lanka,
³Complementary Medicine, Peninsula Medical School, University of Exeter, Exeter and ⁴Complementary and Integrated Medicine Research Unit, University of Southampton, Southampton, UK.
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Correspondence to: Gary J. Macfarlane, Epidemiology Group, School of Medicine and Dentistry, University of Aberdeen, Polwarth Building (Room 1:068), Foresterhill, Aberdeen AB25 2ZD, Scotland, UK.
E-mail: g.j.macfarlane@abdn.ac.uk

*See Appendix 1 for the members of the Arthritis Research Campaign working group on complementary and alternative medicines.

Introduction

FM is a chronic, generalized pain syndrome that affects the musculoskeletal system. It is characterized by widespread pain, the presence of multiple tender points, fatigue and sleep disturbances without any structural or inflammatory cause [1]. It is a common problem among the attendees to rheumatology clinics and usually amounts to 10–20% of new visits [2]. In 1990, the ACR proposed classification criteria for FM: these required chronic widespread pain, i.e. pain on both sides, upper and lower parts of the body and in the axial skeleton for at least 3 months, and presence of tenderness at 11 or more

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Efficacy of Cognitive-Behavioral Therapies in Fibromyalgia Syndrome — A Systematic Review and Metaanalysis of Randomized Controlled Trials

KATHRIN BERNARDY, NICOLE FÜBER, VOLKER KÖLLNER and WINFRIED HÄUSER

J Rheumatol 2010;37;1991-2005

<http://www.jrheum.org/content/37/10/1991>

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Efficacy of Cognitive-Behavioral Therapies in Fibromyalgia Syndrome — A Systematic Review and Metaanalysis of Randomized Controlled Trials

KATHRIN BERNARDY, NICOLE FÜBER, VOLKER KÖLLNER, and WINFRIED HÄUSER

ABSTRACT. *Objective.* We performed the first systematic review with metaanalysis of the efficacy of cognitive-behavioral therapies (CBT) in fibromyalgia syndrome (FM).

Methods. We screened Cochrane Library, Medline, PsychINFO, and Scopus (through June 2009) and the reference sections of original studies and systematic reviews for CBT in FM. Randomized controlled trials (RCT) comparing CBT to controls were analyzed. Primary outcomes were pain, sleep, fatigue, and health-related quality of life (HRQOL). Secondary outcomes were depressed mood, self-efficacy pain, and healthcare-seeking behavior. Effects were summarized using standardized mean differences (SMD).

Results. A total of 14 out of 27 RCT with 910 subjects with a median treatment time of 27 hours (range 6–75) over a median of 9 weeks (range 5–15) were included. CBT reduced depressed mood (SMD -0.24 , 95% CI -0.40 , -0.08 ; $p = 0.004$) at posttreatment. Sensitivity analyses showed that the positive effect on depressed mood could not be distinguished from some risks of bias. There was no significant effect on pain, fatigue, sleep, and HRQOL at posttreatment and at followup. There was a significant effect on self-efficacy pain posttreatment (SMD 0.85 , 95% CI 0.25 , 1.46 ; $p = 0.006$) and at followup (SMD 0.90 , 95% CI 0.14 , 1.66 ; $p = 0.02$). Operant behavioral therapy significantly reduced the number of physician visits at followup (SMD -1.57 , 95% CI -2.00 , -1.14 ; $p < 0.001$).

Conclusion. CBT can be considered to improve coping with pain and to reduce depressed mood and healthcare-seeking behavior in FM. (First Release August 1 2010; J Rheumatol 2010;37:1991–205; doi:10.3899/jrheum.100104)

Key Indexing Terms:

FIBROMYALGIA SYNDROME
COGNITIVE BEHAVIORAL THERAPY
SYSTEMATIC REVIEW

COGNITIVE THERAPY
OPERANT BEHAVIORAL THERAPY
METAANALYSIS

The key symptoms of fibromyalgia syndrome (FM) are chronic widespread pain, fatigue, nonrestorative sleep, and psychological distress^{1,2}. The estimated prevalence of FM in Western

European countries ranges from 2.2% to 6.6%³. Comorbidities with affective or anxiety disorders are common⁴.

Patients with FM use a lot of pharmacological and non-pharmacological therapies, resulting in high costs for health services⁵. Pharmacological and physical therapies are used more frequently than psychotherapeutic treatments. In an Internet survey, only 8% of respondents reported use of cognitive-behavioral therapies (CBT), but over 80% named emotional distress as an aggravating factor⁶.

CBT include interventions that are based on the basic premise that chronic pain is maintained by cognitive and behavioral factors, and that psychological treatment leads to changes in these factors through cognitive (e.g., cognitive restructuring) and/or behavioral (e.g., relaxation training, social skills training) techniques. Different types of CBT can be differentiated by the techniques applied. Mindfulness-based stress reduction (MBSR) is a cognitive therapy that helps individuals to self-manage and reframe worrisome and intrusive thoughts by mindfulness meditation, that is, the nonjudgmental awareness of one's present experience

From the Department of Anaesthesiology, Intensive Care and Pain Therapy, Saarland University Hospital, Homburg/Saar; Department of Psychosomatic Medicine, MediClin Blietal Clinics, Blieskastel; Department of Differential Psychology and Psychodiagnostics, Saarland University, Saarbrücken; Department of Internal Medicine I, Klinikum Saarbrücken, Saarbrücken; and Department of Psychosomatic Medicine, Technische Universität München, München, Germany.

K. Bernardy, PhD, Research Psychologist, Department of Anaesthesiology, Intensive Care and Pain Therapy, Saarland University Hospital, Department of Psychosomatic Medicine, MediClin Blietal Clinics; N. Füber, Psychologist, Department of Differential Psychology and Psychodiagnostics, Saarland University; V. Köllner, MD, Head, Department of Psychosomatic Medicine, MediClin Blietal Clinics; W. Häuser, MD, Head of Subdepartment, Department of Internal Medicine I, Klinikum Saarbrücken, and Department of Psychosomatic Medicine, Technische Universität München.

Address correspondence to Dr. W. Häuser, Klinikum Saarbrücken gGmbH, Winterberg 1, D-66119 Saarbrücken, Germany.

E-mail: whaeuser@klinikum-saarbruecken.de

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Concise Report

Efficacy of hydrotherapy in fibromyalgia syndrome—a meta-analysis of randomized controlled clinical trials

Jost Langhorst¹, Frauke Musial¹, Petra Klose¹ and Winfried Häuser^{2,3}

Objective. To systematically review the efficacy of hydrotherapy in FM syndrome (FMS).

Methods. We screened MEDLINE, PsychInfo, EMBASE, CAMBASE and CENTRAL (through December 2008) and the reference sections of original studies and systematic reviews on hydrotherapy in FMS. Randomized controlled trials (RCTs) on the treatment of FMS with hydrotherapy (spa-, balneo- and thalassotherapy, hydrotherapy and packing and compresses) were analysed. Methodological quality was assessed by the van Tulder score. Effects were summarized using standardized mean differences (SMDs).

Results. Ten out of 13 RCTs with 446 subjects, with a median sample size of 41 (range 24–80) and a median treatment time of 240 (range 200–300) min, were included into the meta-analysis. Only three studies had a moderate quality score. There was moderate evidence for reduction of pain (SMD -0.78 ; 95% CI -1.42 , -0.13 ; $P < 0.0001$) and improved health-related quality of life (HRQOL) (SMD -1.67 ; 95% CI -2.91 , -0.43 ; $P = 0.008$) at the end of therapy. There was moderate evidence that the reduction of pain (SMD -1.27 ; 95% CI -2.15 , -0.38 ; $P = 0.005$) and improvement of HRQOL (SMD -1.16 ; 95% CI -1.96 , -0.36 ; $P = 0.005$) could be maintained at follow-up (median 14 weeks).

Conclusions. There is moderate evidence that hydrotherapy has short-term beneficial effects on pain and HRQOL in FMS patients. There is a risk to over-estimate the effects of hydrotherapy due to methodological weaknesses of the studies and to small trials included in meta-analysis.

KEY WORDS: Fibromyalgia syndrome, Hydrotherapy, Spa therapy, Balneotherapy, Systematic review, Meta-analysis.

Introduction

Hydrotherapy is one non-pharmacological therapy of FM syndrome (FMS) used by up to 75% of the patients [1, 2]. The use of water for medical therapy dates back to ancient cultures from China, Japan and Europe. Balneotherapy (drinking of and/or bathing in medicinal water, bathing in warm or cold water or mud) and spa therapy (drinking of and/or bathing in thermal or mineral water) are different forms of hydrotherapy.

Two qualitative systematic reviews were conducted on the efficacy of hydrotherapy in FMS, which searched the literature until July 2006 [3] and December 2006 [4], respectively. One review included only trials published in English language [3]. In the meantime, further studies on hydrotherapy in FMS have been published, which were not included in systematic reviews so far. To our knowledge, a meta-analysis providing effects sizes of hydrotherapy was not published yet. The aim of our review therefore was to determine the efficacy of hydrotherapy in FMS by updating the search without language restrictions and by a quantitative analysis of data.

Methods

Meta-analysis was performed according to the QUORUM (quality of reporting meta-analyses) guidelines [5].

Data sources and searches

The electronic bibliographic databases screened included MEDLINE, PsychInfo, SCOPUS, the Cochrane Central Register of Controlled Trials (CENTRAL) and CAMBASE (through December 2008). The search strategy for MEDLINE is detailed in supplementary Table 1 (available as supplementary data at *Rheumatology* Online). The search strategy was adapted for each database if necessary. In addition, reference sections of original studies, qualitative systematic reviews on hydrotherapy in FMS [3, 4] and evidence-based guidelines on the management of FMS [6–8] were screened manually. No language restrictions were made.

Study selection

Studies were required to meet the following criteria: (i) any kind of hydrotherapy without exercise; (ii) diagnosis of FMS based on recognized criteria; (iii) randomized controlled trials (RCTs) comparing hydrotherapy with any other intervention or with no intervention; (iv) at least one symptom-specific outcome of the 'key symptoms' of FMS such as pain, fatigue, sleep disturbances, depressed mood and health-related quality of life (HRQOL) [9]; and (v) publication of the study in full paper form.

Data extraction

Two authors screened the titles and abstracts of potentially eligible studies identified by the search strategy detailed above independently. The full text articles were then examined independently by two authors to determine if they met the selection criteria. For the preparation of the meta-analysis, two of the four authors independently extracted data (study characteristics and study results) using standard extraction forms.

Assessment of external validity

The external validity (representativeness of study samples for the FMS population in clinical practice and safety of treatment) was checked by analysing the inclusion and exclusion criteria, the

¹Department of Internal Medicine V (Complementary and Integrative Medicine), University of Duisburg-Essen, Kliniken Essen-Mitte, Essen, ²Department of Internal Medicine I, Klinikum Saarbrücken, Saarbrücken and ³Department of Psychosomatic Medicine, Technische Universität München, München, Germany.

Submitted 20 February 2009; revised version accepted 4 June 2009.

Correspondence to: Winfried Häuser, Klinikum Saarbrücken gGmbH, Winterberg 1, D-66119 Saarbrücken, Germany.
E-mail: whaeuser@klinikum-saarbruecken.de

Multidisciplinary rehabilitation for fibromyalgia and musculoskeletal pain in working age adults (Review)

Karjalainen KA, Malmivaara A, van Tulder MW, Roine R, Jauhiainen M, Hurri H, Koes BW



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Multidisciplinary rehabilitation for fibromyalgia and musculoskeletal pain in working age adults (Review)
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[Intervention Review]

Multidisciplinary rehabilitation for fibromyalgia and musculoskeletal pain in working age adults

Kaija A Karjalainen¹, Antti Malmivaara², Maurits W van Tulder³, Risto Roine⁴, Merja Jauhiainen⁵, Heikki Hurri⁶, Bart W Koes⁷

¹Occupational Medicine, Finnish Institute of Occupational Health, Helsinki, Finland. ²Occupational Medicine, Finnish Office for Health Care Technology Assessment, Helsinki, Finland. ³Department of Health Economics & Health Technology Assessment, Institute of Health Sciences, Faculty of Earth & Life Sciences, VU University, Amsterdam, Netherlands. ⁴Assessment of Technologies, Helsinki and Uusimaa Hospital Group, HUS, Finland. ⁵Knowledge Transfer Team, Finnish Institute of Occupational Health, Helsinki, Finland. ⁶Rehabilitation Centre, ORTON Rehabilitation Centre, Helsinki, Finland. ⁷Department of General Practice, Erasmus MC - University Medical Center Rotterdam, Rotterdam, Netherlands

Contact address: Kaija A Karjalainen, Occupational Medicine, Finnish Institute of Occupational Health, Topeliuksenkatu 41 aA, Helsinki, FIN-00250, Finland. kaija.karjalainen@invalidiliitto.fi.

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ABSTRACT

Background

Non-malignant musculoskeletal pain is an increasing problem in western countries. Fibromyalgia syndrome is an increasing recognised chronic musculoskeletal disorder.

Objectives

The objective of this systematic review was to determine the effectiveness of multidisciplinary rehabilitation for fibromyalgia and widespread musculoskeletal pain among working age adults.

Search methods

An electronic search was conducted and included MEDLINE from 1966, PsycLIT from 1967 and EMBASE from 1980 to April 1998. The Cochrane Musculoskeletal Group Trials Register was searched as well as, the Cochrane Controlled Trials Register (CCTR). The references of identified articles and reviews were checked, studies published in the Finnish medical database Medic from 1978 to 1998 screened and the Science Citation Index searched. Content experts were also contacted for additional or unpublished studies.

Selection criteria

From all references found in our original search, we selected all randomized controlled trials (RCTs) and clinical controlled trials (CCTs). Trials had to assess the effectiveness of multidisciplinary rehabilitation for patients suffering from fibromyalgia and widespread musculoskeletal pain among working age adults. The rehabilitation program was required to be multidisciplinary; that is, it had to consist of a physician's consultation, plus a psychological, social or vocational intervention, or a combination of both.

Data collection and analysis

Four reviewers independently selected the RCTs and CCTs that met the specified inclusion criteria. Two experts in the field of rehabilitation evaluated the relevance and applicability of the findings of the selected studies to actual clinical use. Two other reviewers extracted the data and assessed the main results and the methodological quality of the studies using standardized forms. Finally, a qualitative analysis was performed to evaluate the level of scientific evidence for the effectiveness of multidisciplinary rehabilitation.

Main results

After screening 1808 abstracts, and the references of 65 reviews, we found only seven relevant studies (1050 patients) that met our inclusion criteria. None of these were considered, methodologically, a high quality randomized controlled trial. Four of the included RCTs on fibromyalgia were graded low quality and suggest no quantifiable benefits. The three included RCTs on widespread musculoskeletal pain showed that based on limited evidence, overall, no evidence of efficacy was observed. However, behavioral treatment and stress management appear to be important components. Education combined with physical training showed some positive effects in long term follow up.

Authors' conclusions

We conclude that there appears to be little scientific evidence for the effectiveness of multidisciplinary rehabilitation for these musculoskeletal disorders. However, multidisciplinary rehabilitation is a commonly used intervention for chronic musculoskeletal disorders, which cause much personal suffering and substantial economic loss to the society. There is a need for high quality trials in this field.

PLAIN LANGUAGE SUMMARY

Multidisciplinary rehabilitation for fibromyalgia and musculoskeletal pain in working age adults

Non-malignant musculoskeletal pain is an increasing problem in western countries. Fibromyalgia syndrome is an increasingly recognised chronic musculoskeletal disorder. The main purpose of this systematic review was to determine the effectiveness of multidisciplinary rehabilitation for fibromyalgia and wide spread musculoskeletal pain among working age adults. Patients included in the controlled trials in this review ranged in age from 18-65 years. Seven studies, with 1050 patients were included. The effectiveness of multidisciplinary rehabilitation was graded limited, showing no quantifiable benefit for both fibromyalgia and widespread musculoskeletal pain.

BACKGROUND

Nonmalignant musculoskeletal pain is an increasing problem in western countries (Heliövaara 1993). Fibromyalgia syndrome is an increasingly recognized chronic musculoskeletal disorder (Simms 1994).

Many pharmacological, physical and other therapies (such as assistive devices, hypnosis, relaxation, stress management, therapeutic massage or hydrotherapy), have been widely used, although scientific evidence of their effectiveness is still lacking. The benefits of these treatments are often temporary. Prolonged pain tends to develop into a combination of physical, psychological and social disabilities. For that reason the physical rehabilitation for musculoskeletal disorders has been combined with psychological, behavioral and educational interventions (Allegrante 1996). The conceptual basis for this kind of rehabilitation lies on the bio-psycho-social model of illness. The multidisciplinary treatment is prac-

ticed in pain clinics or rehabilitation centers, which have rapidly increased in numbers over the last decades (Flor 1992). Today, the bio-psycho-social model is also applied in outpatient rehabilitation.

Multidisciplinary treatment programs require substantial staff and financial resources from the health care system. The indirect costs burden the employers, insurance companies and patients. The value of the multidisciplinary treatment has often been questioned because of the lack of data on its effectiveness and cost-effectiveness. Two meta-analyses on the effectiveness of multidisciplinary pain treatment have been published (Flor 1992, Cutler 1994), but both lack information of the most recent trials.

This review is series of four systematic reviews, on effectiveness of multidisciplinary rehabilitation on common musculoskeletal disorders among working age adults.

Open Wound of Eardrum

Question: should Line 456 OPEN WOUND OF EAR DRUM be merged with Line 502 CHRONIC OTITIS MEDIA?

Question source: HERC staff

Issue: line 456 has a single diagnosis (872.61, Open wound of ear drum, without mention of complication). Other diagnoses involving open damage to the ear drum (ruptured ear drum) appear on line 502. Line 502 has all the repair CPT codes required.

HERC Staff Recommendation:

- 1) Move ICD-9 872.61 to line 502
 - a. ICD-10 S09.20XA
- 2) Delete line 456

Section 6.0

Coverage guidances

CG - UPPER ENDOSCOPY FOR GASTROESOPHAGEAL REFLUX DISEASE (GERD) AND DYSPESIA SYMPTOMS

Question: How should the Coverage Guidance - *UPPER ENDOSCOPY FOR GASTROESOPHAGEAL REFLUX DISEASE (GERD) AND DYSPESIA SYMPTOMS* be applied to the Prioritized List?

Question source: Health Technology Assessment Subcommittee

Current Prioritized List Status

- 1) Diagnostic codes:
 - a. ICD-9 536.8 (Dyspepsia and other specified disorders of function of stomach) is on line 551 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS
 - b. ICD-9 530.10 (Esophagitis, unspecified), 530.11 (Reflux esophagitis) and 530.81 (Esophageal reflux) are on line 411 ESOPHAGITIS; ESOPHAGEAL AND INTRAESOPHAGEAL HERNIAS; SURGICAL TREATMENT and 423 ESOPHAGITIS; MEDICAL THERAPY
 - c. ICD-9 787.2x (Dysphagia) is on line 78 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES
 - d. ICD-9 787.1 (Heartburn) is on the Diagnostic List
- 2) Treatment codes:
 - a. Most upper endoscopy codes for diagnosis/biopsy (CPT 43200, 43202, etc.) are on the Diagnostic List
 - b. Some upper endoscopy codes for treatment of masses, bleeding, etc. are on lines 411 and 423
 - c. No upper endoscopy CPT codes are on lines 78 or 551
- 3) HTAS approved 6/6/13 Draft Coverage Guidance Box

Upper endoscopy for uninvestigated dyspepsia or GERD symptoms is not recommended for coverage in patients less than 50 years of age unless the patient has persistent symptoms following advice on lifestyle modifications and completion of an appropriate course of twice daily PPI therapy or an H. pylori test and treat protocol (*strong recommendation*).

Upper endoscopy for uninvestigated dyspepsia or GERD symptoms is recommended for coverage in patients at least 50 years of age (*strong recommendation*).

Upper endoscopy is recommended for coverage in patients with troublesome dysphagia, regardless of age or prior upper endoscopy.

In the absence of significant new symptoms, repeat upper endoscopy is not recommended for coverage for patients with dyspepsia or GERD after non-malignant findings (with the exception of Barrett's esophagus) on initial upper endoscopy (*weak recommendation*).

CG - UPPER ENDOSCOPY FOR GASTROESOPHAGEAL REFLUX DISEASE (GERD) AND DYSPEPSIA SYMPTOMS

Note: This guidance does not apply to coverage of upper endoscopy for patients presenting with “alarm symptoms” including, but not limited to, iron deficiency anemia or weight loss.

HERC Staff Recommendations:

- 1) **Add a new diagnostic guideline:**

DIAGNOSTIC GUIDELINE DX UPPER ENDOSCOPY FOR GERD OR DYSPEPSIA SYMPTOMS

Upper endoscopy for uninvestigated dyspepsia or GERD symptoms is covered for

- 1) Patients less than 50 years of age with persistent symptoms following advice on lifestyle modifications and completion of an appropriate course of twice daily PPI therapy or an H. pylori test and treat protocol.
- 2) Patients 50 years of age and older
- 3) Patients with troublesome dysphagia, regardless of age or prior upper endoscopy.
- 4) Patients with “alarm symptoms” including, but not limited to, iron deficiency anemia or weight loss

Upper endoscopy is not covered for patients with previous upper endoscopy with non-malignant findings (other than Barrett’s esophagus) in the absence of significant new symptoms.

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: UPPER ENDOSCOPY FOR GASTROESOPHAGEAL REFLUX DISEASE (GERD) AND DYSPESIA SYMPTOMS

DRAFT FOR VbBS Meeting Materials 10/10/2013

HERC COVERAGE GUIDANCE

Upper endoscopy for uninvestigated dyspepsia or GERD symptoms is not recommended for coverage in patients less than 50 years of age unless the patient has persistent symptoms following advice on lifestyle modifications and completion of an appropriate course of twice daily PPI therapy or an H. pylori test and treat protocol (*strong recommendation*).

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Note: This guidance does not apply to coverage of upper endoscopy for patients presenting with "alarm symptoms" including, but not limited to, iron deficiency anemia or weight loss.

Note: Definitions for strength of recommendation are provided in Appendix A GRADE Element Description

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Health Technology Assessment Subcommittee. In addition, coverage

guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

EVIDENCE SOURCE

Liu, R., Kriz, H., Thielke, A., Vandegriff, S., & King, V. (2012). *Upper endoscopy for gastroesophageal reflux disease (GERD) and upper gastrointestinal (GI) symptoms*. Olympia: Washington State Health Authority Health Technology Assessment Program. Retrieved February 21, 2013, from <http://www.hta.hca.wa.gov/gerd.html>

The summary of evidence in this document is derived directly from this evidence source, and portions are extracted verbatim.

SUMMARY OF EVIDENCE

Clinical Background

Gastroesophageal reflux disease (GERD) is the most common outpatient gastrointestinal diagnosis in the United States, with a prevalence of 10% to 58.3% and an annual incidence of 0.38% to 0.45%. The Montreal consensus panel, an international Consensus Group tasked with developing a global definition and classification of GERD, reached strong consensus in defining GERD as “a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications”. Common symptoms of GERD include heartburn (defined as a burning sensation behind the breastbone), regurgitation and chest pain. Obesity; the presence of a hiatal hernia; and the use of estrogen, nitrates, anticholinergics, and tobacco products are considered risk factors for GERD. Gastroesophageal reflux disease can lead to a decreased quality of life and to more severe conditions such as esophagitis, Barrett's esophagus, and adenocarcinoma of the esophagus.

Dyspepsia is estimated to range in prevalence in the United States from 2.9 to 34.4%. The Rome III Committee defines dyspepsia as having one or more of the following symptoms: epigastric pain or burning; postprandial fullness; and/or early satiety. Other dyspeptic symptoms may include nausea and vomiting, upper abdominal bloating, heart burn, and regurgitation. Dyspepsia symptoms are distinguished from GERD as not being “troublesome” enough, referring to the Montreal definition of GERD; however, many authors have used the terms interchangeably.

The signs and symptoms of GERD, dyspepsia, and other more severe conditions such as Barrett's esophagus, can be very similar, and diagnostic procedures can be used to establish a diagnosis and rule out other possible conditions. Diagnostic procedures for dyspepsia and GERD can include questionnaires, empiric therapeutic trial, pH monitoring, upper endoscopy, and/or double contrast barium swallow. Empiric

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therapeutic trial is a commonly employed strategy for patients presenting with GERD. This includes both an empiric trial of proton pump inhibitors (PPI) and test-and-treat for *Helicobacter pylori* (*H. pylori*). An empiric trial of PPIs typically includes twice daily dosing for four weeks, and a daily dose of 40 to 80mg of omeprazole is the most common PPI regimen used in clinical empiric therapy studies. The sensitivity and specificity of this PPI test ranges from 62 to 92% and 36 to 100%, respectively.

Evidence Review

Effectiveness of Early Treatment Strategies

With regard to the effectiveness of early treatment strategies for GERD that include upper endoscopy compared with empiric medical management, one good quality systematic review including two separate meta-analyses was identified. One evaluated early endoscopy versus empiric PPI and the other evaluated early endoscopy versus test-and-treat for *H. pylori*. The first meta-analysis included five RCTs and found no difference in symptomatic cure at 12 months between endoscopy and PPI arms. The second meta-analysis, also including five RCTs, was first done by pooling trial-level data. This analysis found no difference in effect (RR 0.95, 95% CI 0.79 to 1.15), but a high degree of statistical heterogeneity. When an alternate analysis of these same five studies was done using individual patient data, there was no longer statistical heterogeneity and a small but statistically significant benefit to upper endoscopy emerged (OR 0.75, 95% CI 0.58 to 0.96; RR 0.95, 95% CI 0.92 to 0.99).

A single fair quality prospective cohort study of 70 patients found that 24-hour pH monitoring is the most accurate single diagnostic test for GERD, when a concordance of three separate tests (omeprazole challenge, endoscopy, histology, pH monitoring) is taken as the gold standard. However, the authors note that there are barriers to its widespread use including invasiveness, cost, and availability. A serial application of an omeprazole challenge test, endoscopy, and finally histopathology achieves a sensitivity of 100% for GERD diagnosis.

Overall, considering all the available evidence from the systematic review plus the cohort study, there does not appear to be a clinically relevant benefit of prompt upper endoscopy over test and treat strategies or empiric PPI therapy for uninvestigated GERD symptoms in the primary care setting. (*Overall strength of evidence: High*)

Indications for Early Endoscopy

When considering whether there are clinical signs and symptoms that may be useful to identify patients for whom early endoscopy improves health outcomes, one good quality systematic review of 57,363 patients in 17 prospective cohort studies was identified.

They found that alarm symptoms¹, clinical opinion, and computer modeling programs based on symptom questionnaires were all unreliable predictors of gastrointestinal malignancy. Sensitivity ranged from 0% to 83% while specificity varied from 40% to 98%.

A good quality prospective cohort study found cancer in 0.9% of patients presenting with uncomplicated dyspepsia (i.e., without alarm symptoms) and the findings suggest that risk is correlated with age greater than 35 for males and greater than 57 for females. A fair quality prospective cohort study determined that American Society of Gastroenterologists (ASGE) guideline criteria (indications for endoscopy) were poorly correlated with clinically relevant endoscopic findings, although having a guideline indication does marginally increase the pre-test probability of endoscopy (from 45% to 47%), while not having one lowers it (from 45% to 29%). A second fair-quality prospective cohort study in the setting of open-access endoscopy found that 15% of the patients with esophagogastric carcinoma did not present with alarm symptoms and may have suffered delayed diagnosis without early endoscopy; however, there was an unusually high prevalence (3%) of cancer in the study population. Finally, a fair-quality prospective cohort study of primary care patients with uninvestigated dyspepsia found that Barrett's esophagus was most likely in patients who were male, greater than 50 years old, had symptoms of at least 5 to 10 years duration, and suffered predominantly from reflux.

The authors of the systematic review noted above suggest that, in the absence of compelling predictors, the concept of "alarm symptoms" should not be abandoned at this time. They suggest age greater than 55 as "the most logical alternative strategy... because the incidence of upper GI malignancy is negligible in Western populations at younger ages and only rises in prevalence above the age of 55 years." In contrast, the authors of the good quality cohort study suggest that age should be lower (35) for males and could be higher (57) for females. (*Overall strength of evidence: Moderate*)

Repeat Endoscopy

With regard to whether there are diagnoses for which repeat endoscopy is indicated, only one study, a prospective cohort study of good quality, addressed the question. This study evaluated the utility of repeat endoscopy in patients who initially presented with dyspeptic symptoms and had non-malignant endoscopic findings. About a third of these patients underwent a subsequent endoscopy within nine years of the index study. The results of these later endoscopies are not known; however, patients who had further endoscopy were neither more nor less likely than other patients to be symptomatic eight to nine years after the index study ($\chi^2=0.6$, $df=1$, $p > 0.05$). Overall, evidence is

¹ Weight loss, dysphagia, anemia

insufficient to suggest repeat endoscopy to any patients with initial dyspepsia who have non-malignant findings on their index endoscopy. (*Overall strength of evidence: Low*)

Harms of Endoscopy

None of the included studies addressed harms. According to the authors of one economic evaluation, most harms of endoscopy are cardiorespiratory in nature; that is, related to the procedure sedation rather than the endoscope itself. These authors used a 0.02% incidence of severe harms and modeled their economic assumptions on the surgical repair of perforation. No data was identified on harms associated with empiric acid-suppression or *H. pylori* test-and-treat. (*Overall strength of evidence: Insufficient*)

Subpopulations

Age was the only factor associated with differential effectiveness in one good quality meta-analysis. The authors of this study performed subgroup analyses based on age, gender, predominant symptom, and presence of *H. pylori*. There was a small but statistically significant benefit of endoscopy in patients 50 years of age and older (RR=0.90, 95% CI 0.82 to 1.00, $p < 0.05$); no other associations were found. A good-quality prospective cohort study found that patients with malignancy were on average 20 years older than patients without malignancy ($p < 0.001$). A fair-quality prospective cohort study also found increasing prevalence of malignancy with rising age. In a good quality economic evaluation simulation model, relative effectiveness of interventions was similar, but resulted in slightly fewer additional quality adjusted life years (QALY) in hypothetical 30 year olds than in hypothetical 60 year olds. A poor quality retrospective chart review of VA patients failed to find any correlation between significant endoscopic findings (Barrett's esophagus and/or erosive esophagitis) and age, gender, race, or NSAID use. (*Overall strength of evidence: Moderate [Age], Insufficient [All others]*)

Cost-effectiveness of Endoscopy Compared to Other Treatment Strategies

With the exception of empiric therapy for US 30 year olds, all five good quality studies, one of two fair quality studies, and one of three poor quality studies favored *H. pylori* test-and-treat as the most cost-effective strategy for adults with uninvestigated symptoms of dyspepsia and/or GERD. Only two studies, both of good quality, evaluated the cost-effectiveness of different management strategies for new upper gastrointestinal symptoms in a US population. In a simulation model, empiric PPI was the strategy of choice for 30 year old patients, and test-and-treat for *H. pylori* was the most cost-effective intervention for 60 year olds. A decision analysis looked only at patients less than 45 years of age, and determined that adding a 6-week trial of PPI to the test-and-treat strategy improved its cost-effectiveness. A good quality economic evaluation of Canadian individual patient data concluded that no one strategy was the most clearly cost-effective, but at a clinically relevant willingness-to-pay threshold of CAN\$30,000 to 70,000 per QALY, omeprazole treatment based on the CanDys protocol (which

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incorporates test-and-treat for those without heartburn or reflux as the predominant symptom) was the most cost-effective. Two other good quality models also favored the test-and-treat approach, along with one fair and one poor quality RCT. One fair quality decision analysis favored a screening questionnaire followed by prompt endoscopy for high-risk patients. Two poor quality RCTs found empiric PPI to be the most cost-effective alternative, but did not include comparison to *H. pylori* testing and treatment. There were no economic studies that found prompt endoscopy to be the most cost-effective intervention. (*Overall strength of evidence: Moderate*)

[\[Evidence Source\]](#)

Evidence Summary

Overall, the evidence does not point to a clinically relevant benefit of prompt upper endoscopy over test-and-treat strategies or empiric PPI therapy for uninvestigated GERD symptoms in the primary care setting. Alarm symptoms, clinical opinion, and computer modeling programs based on symptom questionnaires are all unreliable predictors of gastrointestinal malignancy. The harms of endoscopy, or of any of the treatment strategies for GERD or dyspepsia, have not been well documented in this literature base. There is an increasing prevalence of malignancy with rising age, and there may be a small benefit of endoscopy over other initial treatment strategies in patients over 50 based on one trial. Test-and-treat for *H. pylori* is likely the most cost-effective strategy for adults with uninvestigated symptoms of dyspepsia and/or GERD.

GRADE-INFORMED FRAMEWORK

The HERC develops recommendations by using the concepts of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for carrying out the steps involved in developing recommendations. There are four elements that determine the strength of a recommendation, as listed in the table below. The HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Balance between desirable and undesirable effects, and quality of evidence, are derived from the evidence presented in this document, while estimated relative costs, values and preferences are assessments of the HERC members.

Indication	Balance between desirable and undesirable effects	Quality of evidence*	Resource Allocation	Values and preferences	Coverage Recommendation
Endoscopy as initial evaluation for new onset GERD or dyspepsia in patients under 50 or 55	No net benefit compared to other treatment strategies	High	Other treatment strategies are less costly	Low variability. Most would want to avoid endoscopy; some would prefer definite diagnosis before treatment	Upper endoscopy for uninvestigated dyspepsia or GERD symptoms is not recommended for coverage in patients less than 50 years of age unless the patient has completed an appropriate course of PPI therapy or an H. pylori test and treat protocol (strong recommendation).
Endoscopy as initial evaluation for new onset GERD or dyspepsia in patients over 50 or 55	Small net benefit compared to other treatment strategies	Moderate	Endoscopy moderately more costly	Moderate variability	Upper endoscopy for uninvestigated dyspepsia or GERD symptoms is recommended for coverage in patients at least 50 years of age (strong recommendation)

Indication	Balance between desirable and undesirable effects	Quality of evidence*	Resource Allocation	Values and preferences	Coverage Recommendation
Repeat endoscopy after initial endoscopy for GERD with non-malignant findings	No apparent benefit, small harms	Insufficient	Endoscopy moderately more costly	Moderate variability	In the absence of significant new symptoms, repeat upper endoscopy is not recommended for coverage for patients with dyspepsia or GERD after non-malignant findings (with the exception of Barrett's esophagus) on initial upper endoscopy (weak recommendation).

*The Quality of Evidence rating was assigned by the primary evidence source, not the HERC Subcommittee

Note: GRADE framework elements are described in Appendix A

POLICY LANDSCAPE

Eight quality measures were identified when searching the [National Quality Measures Clearinghouse](#). Five are sponsored by the American Gastroenterological Association Institute, while three are sponsored by the Australian Council on Healthcare Standards. None have been endorsed by the National Quality Forum. The five American measures are listed below:

1. Gastroesophageal reflux disease (GERD): percentage of patients aged 18 and older with the diagnosis of GERD who have been prescribed chronic proton pump inhibitor (PPI) or histamine H₂ receptor antagonist (H₂ RA) therapy who received an assessment of their GERD symptoms within 12 months
2. Gastroesophageal reflux disease (GERD): percentage of patients aged 18 seen for an initial evaluation of GERD who did not have a barium swallow test ordered
3. Gastroesophageal reflux disease (GERD): percentage of patients aged 18 and older with the diagnosis of GERD, seen for an initial evaluation, who were assessed for the presence or absence of the following alarm symptoms: involuntary weight loss, dysphagia, and GI bleeding
4. Gastroesophageal reflux disease (GERD): percentage of patients aged 18 and older with the diagnosis of GERD or heartburn whose endoscopy report indicates a suspicion of Barrett's esophagus who had a forceps biopsy performed
5. Gastroesophageal reflux disease (GERD): percentage of patients aged 18 and older seen for an initial evaluation with at least one alarm symptom who were either referred for upper endoscopy or had an upper endoscopy performed

COMMITTEE DELIBERATIONS – HTAS

HTAS reviewed this topic at its meetings June 25 and September 23, 2013. They made the following decisions:

- Add a disclaimer that the coverage guidance does not apply to patients with alarm symptoms of iron-deficiency anemia and weight loss (hematemesis was also considered but dismissed).
- Based on professional guidelines provided in the public comment period, recommended noncoverage for repeat endoscopy after the first endoscopy finds no evidence of malignancy or Barrett's esophagus, unless there are significant new symptoms.
- Require advice on lifestyle modifications and a trial of twice daily proton pump inhibitor therapy.

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- Add a statement clarifying that endoscopy is covered for symptoms of troublesome dysphagia regardless of age.

COMMITTEE DELIBERATIONS – VBBS

Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

Appendix A. GRADE Element Descriptions

Element	Description
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Resource allocation	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted

Strong recommendation

In Favor: The subcommittee is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Against: The subcommittee is confident that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Weak recommendation

In Favor: the subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Against: the subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Quality of evidence across studies for the treatment/outcome

High = Further research is very unlikely to change our confidence in the estimate of effect.

Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low = Any estimate of effect is very uncertain.

Appendix B. Applicable Codes

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
530.1	Esophagitis
530.11	Reflux esophagitis
530.12	Acute esophagitis
530.19	Other esophagitis
530.2	Ulcer of esophagus
530.21	... with bleeding
530.3	Stricture and stenosis of esophagus
530.81	Esophageal reflux
530.85	Barrett's esophagus
530.89	Other specified disorders of esophagus
530.9	Unspecified disorder of esophagus
535	Gastritis and duodenitis
535.0	Acute gastritis
535.2	Gastric mucosal hypertrophy
535.3	Alcoholic gastritis
535.4	Other specified gastritis
535.5	Unspecified gastritis and gastroduodenitis
536.2	Persistent vomiting
536.8	Dyspepsia and other specified disorders of function of stomach
536.9	Unspecified functional disorder of stomach
786.5	Chest pain
786.59	Other chest pain
787.1	Heartburn
787.2	Dysphagia
787.21	...oral phase
787.22	... oropharyngeal phase
787.23	... pharyngeal phase
787.24	... pharyngoesophageal phase
787.29	Other dysphagia
789	Other symptoms involving abdomen and pelvis
789.06	... epigastric
789.07	... generalized
789.09	... other specified site
ICD-9 Volume 3 (Procedure Codes)	
42.23	Other esophagoscopy
42.24	Closed [endoscopic] biopsy of esophagus
44.13	Other gastroscopy
44.14	Closed [endoscopic] biopsy of stomach

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CODES	DESCRIPTION
45.13	Other endoscopy of small intestine
45.14	Closed [endoscopic] biopsy of small intestine
45.16	Esophagogastroduodenoscopy [EGD] with closed biopsy
CPT Codes	
43200	Esophagoscopy, rigid or flexible; diagnostic, with or without collection of specimen(s) by brushing or washing (separate procedure)
43202	...with biopsy, single or multiple
43235	Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; diagnostic, with or without collection of specimen(s) by brushing or washing (separate procedure)
43239	...with biopsy, single or multiple
HCPCS Level II Codes	
None	

Note: Inclusion on this list does not guarantee coverage

Appendix C. HERC Guidance Development Framework

Endoscopy for Evaluation of Dyspepsia/GERD under Age 50/55 (Prior to PPI or Test and Treat)



Center for Evidence-based Policy

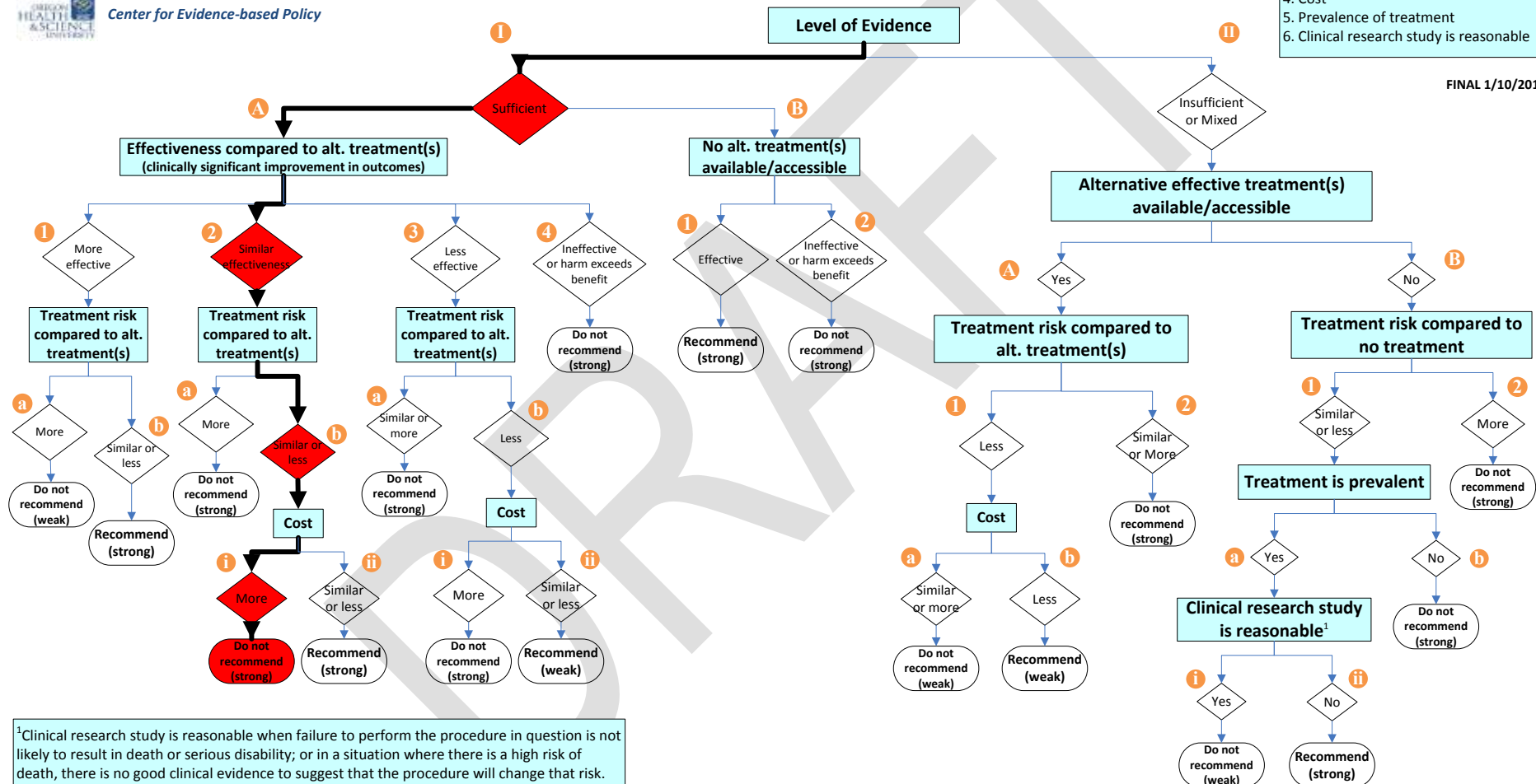
HERC Guidance Development Framework

Refer to HERC Guidance Development Framework Principles for additional considerations

Decision Point Priorities

1. Level of evidence
2. Effectiveness & alternative treatments
3. Harms and risk
4. Cost
5. Prevalence of treatment
6. Clinical research study is reasonable

FINAL 1/10/2013



Endoscopy for Evaluation of Dyspepsia/GERD after age 50/55 (Compared to PPI or Test and Treat)



Center for Evidence-based Policy

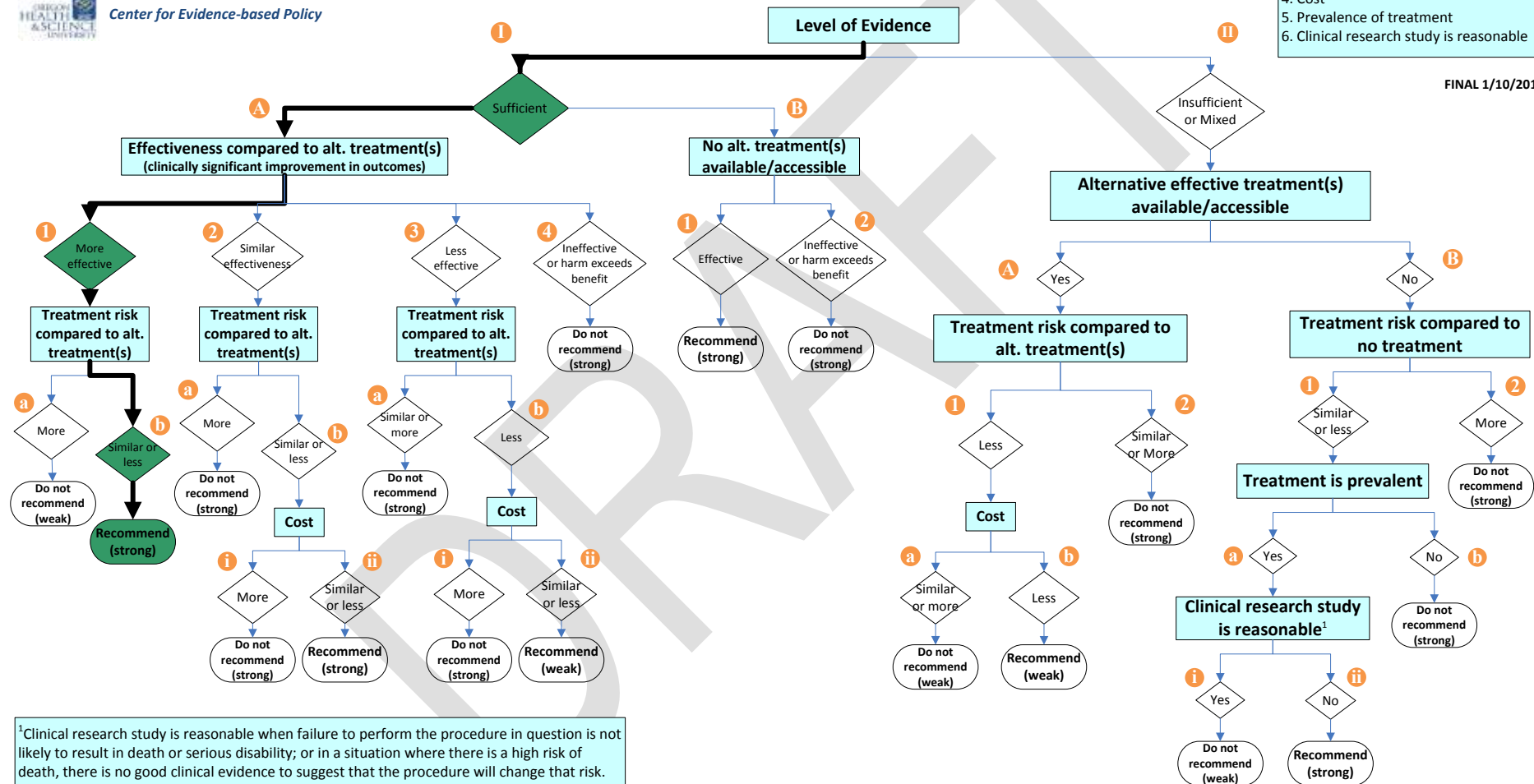
HERC Guidance Development Framework

Refer to HERC Guidance Development Framework Principles for additional considerations

Decision Point Priorities

1. Level of evidence
2. Effectiveness & alternative treatments
3. Harms and risk
4. Cost
5. Prevalence of treatment
6. Clinical research study is reasonable

FINAL 1/10/2013



Repeat endoscopy after initial endoscopy for GERD with non-malignant findings (except Barrett's esophagus and in the absence of new symptoms)



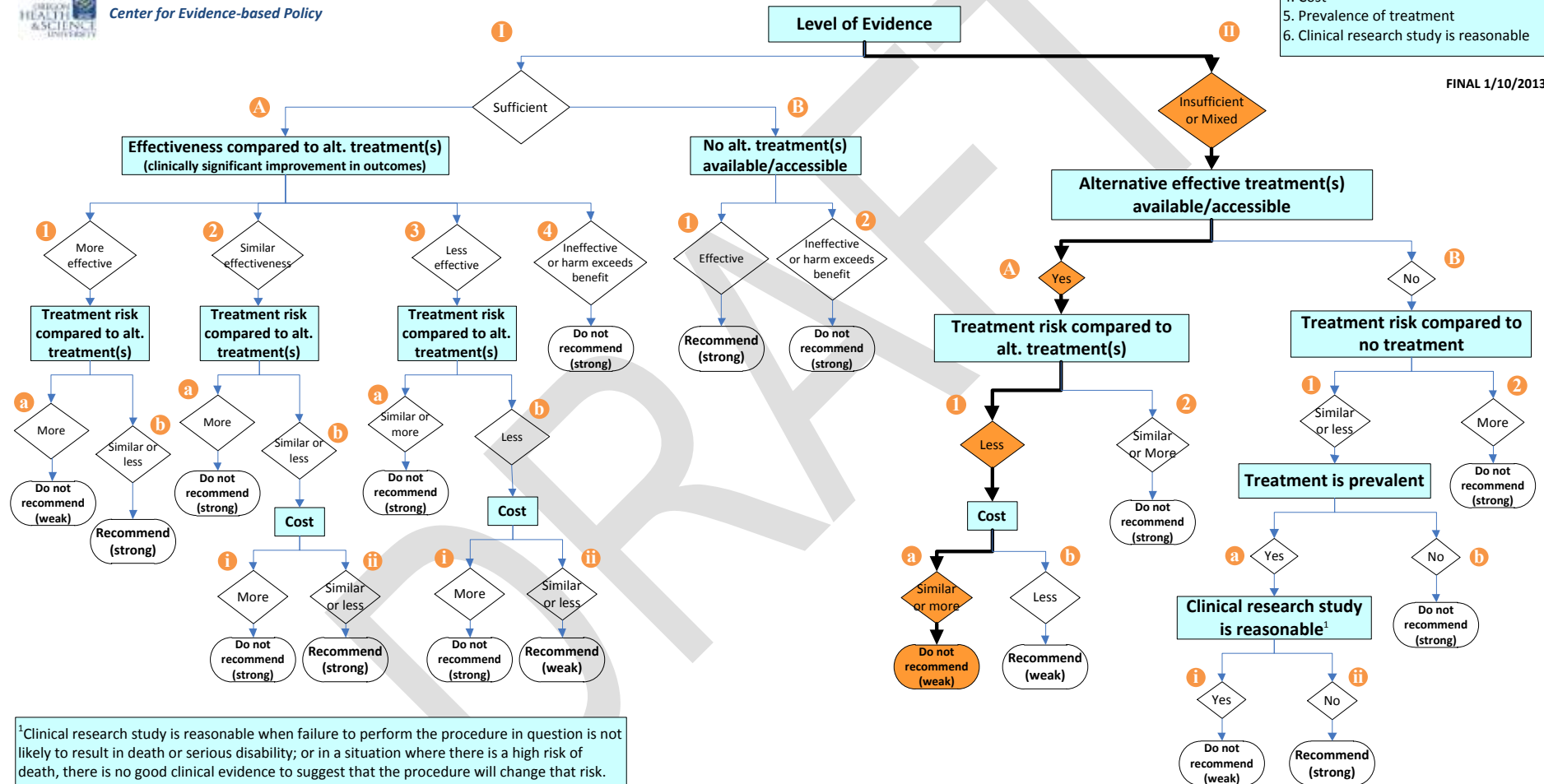
Center for Evidence-based Policy

HERC Guidance Development Framework

Refer to HERC Guidance Development Framework Principles for additional considerations

- Decision Point Priorities**
1. Level of evidence
 2. Effectiveness & alternative treatments
 3. Harms and risk
 4. Cost
 5. Prevalence of treatment
 6. Clinical research study is reasonable

FINAL 1/10/2013



HERC Coverage Guidance – Upper Endoscopy for Gastroesophageal Reflux Disease (GERD) and Dyspepsia Symptoms

Disposition of Public Comments

Commenter:

Drew B. Schembre, MD, Gastroenterologist, Swedish, Seattle, WA, *HERC-appointed Expert*

Comments Grouped by Topic

#	Comment	Disposition
1	Here are some recent guidelines from three separate GI societies regarding diagnostic approaches to GERD and dyspepsia. There are well reasoned decision trees that are worth reviewing. There are additional cost analyses that are interesting. I believe these support my contention that recognition of alarm symptoms, age > 50 and persistent GERD symptoms after a 2 week trial of treatment warrant upper endoscopy.	Thank you for this additional information.
2	American Society for Gastrointestinal Endoscopy. (2007). Role of endoscopy in the management of GERD. <i>Gastrointestinal Endoscopy</i> , 66(2), 219-224. <i>Rated poor quality by CEBP¹</i>	Recommendations pertinent to this guidance include the following: “Endoscopy is recommended for patients who have symptoms suggesting complicated GERD or alarm symptoms (2A).” 2A recommendation is described as intermediate strength; unclear benefit; based on RCTs Alarm symptoms are listed as GERD symptoms persistent or progressive despite medical therapy (length of therapy not specified), dysphagia/odynophagia, involuntary weight loss (>5%), GI bleeding/anemia, presence of mass/stricture/ulcer, persistent vomiting, suspected extra-esophageal manifestations of GERD (latter indication contradicted by Katz and Kahrilas). “Endoscopy should be considered in patients at risk for Barrett’s esophagus (BE) (level of evidence = 2C).” 2C recommendation is described as very weak recommendation, alternative approaches likely to be better under some circumstances; unclear benefits; based on observational studies. Risk factors for BE listed as prolonged (>5 years) GERD symptoms, white race, male sex, age >

¹ The Center for Evidence-based Policy (CEbP) assesses the methodological quality of guidelines using an instrument adapted from the Appraisal of Guidelines Research and Evaluation (AGREE) Collaboration (<http://www.agreetrust.org/resource-centre/practice-guidelines/>). Guideline are assigned a rating of good, fair, poor, based on its adherence to recommended methods and potential for biases.

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#	Comment	Disposition
		50, + family history No evidence provided to support screening for those at risk of BE (white race, male sex) and evidence to support other alarm symptoms also not provided. No change made to guidance recommendation.
3	Katz, P.O., Gerson, L.B., & Vela, M.F. (2013). Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease. <i>American Journal of Gastroenterology</i>, 108, 308-328. doi: 10.1038/ajg.2012.444 <i>Rated poor quality by CEBP</i>	Recommendations pertinent to this guidance include the following: “Upper endoscopy is not required in the presence of typical GERD symptoms. Endoscopy is recommended in the presence of alarm symptoms and for screening of patients at high risk for complications. Repeat endoscopy is not indicated in patients without Barrett’s esophagus in the absence of new symptoms.” Alarm symptoms are specified as dysphagia, but not otherwise described. Those at high risk for complications are likewise not defined. “Upper endoscopy should be performed in refractory patients with typical or dyspeptic symptoms principally to exclude non-GERD etiologies.” Definition of refractory not provided, but author notes that poor compliance and inappropriate dosing are significant factors in lack of response to PPI and should be corrected first. Eight week course of PPIs is recommended as initial treatment. “Upper endoscopy is not recommended as a means to establish a diagnosis of GERD-related asthma, chronic cough, or laryngitis.” Coverage guidance recommendation revised to recommend against coverage of repeat endoscopy in the absence of significant new symptoms or presence of BE.
4	Talley, N.J., Vakil, N., & the Practice Parameters Committee of the American College of Gastroenterology. (2005). Guidelines for the Management of Dyspepsia. <i>American Journal of Gastroenterology</i>, 100, 2324-2337. doi: 10.1111/j.1572-0241.2005.00225.x <i>Rated poor quality by CEBP</i>	Recommendations pertinent to this guidance include the following: Patients with dyspepsia should undergo EGD if they are > 55 or have alarm symptoms, defined as: • Bleeding or anemia • Early satiety • Unexplained weight loss > 10% of body weight • Progressive dysphagia or odynophagia

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#	Comment	Disposition
		• Persistent vomiting • Personal or family history of esophagogastric malignancy • History of peptic ulcer • Lymphadenopathy • Abdominal mass Repeat EGD is not recommended unless completely new symptoms or alarm features develop. Use of antisecretory therapy can mask a cancer at endoscopy, but does not appear to alter the outcome. Refractory GERD not defined, but recommendation is for initial 4-8 week course of PPI. Coverage guidance recommendation revised to recommend against coverage of repeat endoscopy in the absence of significant new symptoms or presence of BE.
5	Kahrilas, P.J., Shaheen, N.J., Vaezi, M.F., Hiltz, S.W., Black, E., Modlin, I.M., et al. (2008). American Gastroenterological Association medical position statement on the management of gastroesophageal reflux disease. <i>Gastroenterology</i>, 135(4), 1383-1391, 1391.e1-5. <i>Rated good quality by CEBP</i>	Recommendations pertinent to this guidance include the following: <i>How Do Antisecretory Therapies Compare in Efficacy and Under What Circumstances Might One Be Preferable to Another? What Is an Acceptable Upper Limit of Empirical Therapy in Patients With Suspected Typical Esophageal GERD Syndromes Before Performing Esophagogastroduodenoscopy?</i> PPIs are recommended for initial empiric treatment (Grade A). Authors state “Patients whose heartburn has not adequately responded to twice-daily PPI therapy should be considered treatment failures, making that a reasonable upper limit for empirical therapy.” However, length of initial trial of PPIs is not specified. <i>What Is the Role and Priority of Diagnostic Tests (Endoscopy With or Without Biopsy, Esophageal Manometry, Ambulatory pH Monitoring, Impedance-pH Monitoring) in the Evaluation of Patients With Suspected Esophageal GERD Syndromes?</i> Grade B: recommended with fair evidence that it improves important outcomes I. Endoscopy with biopsy for patients with an esophageal GERD syndrome with

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Disposition of Public Comments

#	Comment	Disposition
		troublesome dysphagia. II. Endoscopy to evaluate patients with a suspected esophageal GERD syndrome who have not responded to an empirical trial of twice-daily PPI therapy. Grade Insuff: no recommendation, insufficient evidence to recommend for or against I. Using alarm symptoms (other than troublesome dysphagia) as a screening tool to identify patients with GERD at risk for esophageal adenocarcinoma. <i>Does GERD Progress in Severity, Such That Symptomatic Patients Without Esophagitis Develop Esophagitis and Barrett's Metaplasia, or Are These Distinct Disease Manifestations That Do Not Exist Along a Continuum? If Patients Do Progress, at What Rate Does This Occur, and Does It Warrant Endoscopic Monitoring?</i> Grade D: recommend against, fair evidence that it is ineffective or harms outweigh benefits I. Routine endoscopy in subjects with erosive or nonerosive reflux disease to assess for disease progression. <i>What Is the Role of Endoscopy in Longterm Management of Patients With GERD, and Under What Circumstances Should Mucosal Biopsy Specimens Be Obtained When Endoscopy Is Performed?</i> Grade B: recommended with fair evidence that it improves important outcomes I. Endoscopy with biopsy for patients with an esophageal GERD syndrome with troublesome dysphagia. Grade Insuff: no recommendation, insufficient evidence to recommend for or against I. Routine upper endoscopy in the setting of chronic GERD symptoms to diminish the risk of death from esophageal cancer. II. Endoscopic screening for Barrett's esophagus and dysplasia in adults 50 years or older with >5–10 years of heartburn to reduce mortality from esophageal adenocarcinoma. Coverage guidance recommendation revised to recommend against coverage of repeat endoscopy in the absence of significant new symptoms or presence of BE.
6	American Society for Gastrointestinal Endoscopy. (2012). The role of endoscopy in Barrett's esophagus and other premalignant conditions of the esophagus. <i>Gastrointestinal Endoscopy</i> , 76(6), 1087-1094.	Recommendations pertinent to this guidance include the following: 1. Endoscopic screening for BE can be considered in select patients with multiple risk factors for Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC), but patients should

HERC Coverage Guidance – Upper Endoscopy for Gastroesophageal Reflux Disease (GERD) and Dyspepsia Symptoms Disposition of Public Comments

#	Comment	Disposition
	<i>Rated poor quality by CEBP</i>	be informed that there is insufficient evidence to affirm that this practice prevents cancer or prolongs life. Risk factors are defined as male sex, white race, age > 50, + family history, increased duration of reflux symptoms, smoking and obesity. 2. We recommend no further endoscopic screening for BE after a screening examination with negative findings. Coverage guidance recommendation revised to recommend against coverage of repeat endoscopy in the absence of significant new symptoms or presence of BE.

CG – Prenatal Genetic Testing

Question: How should the Coverage Guidance – *Prenatal Genetic Testing* be applied to the Prioritized List?

Question source: Evidence-based Guideline Subcommittee

HERC COVERAGE GUIDANCE

The following are recommended for coverage (*weak recommendation*):

- Genetic counseling for high risk women who have family history of inheritable disorder or carrier state, ultrasound abnormality, previous pregnancy with aneuploidy, or elevated risk of neural tube defect
- Genetic counseling prior to CVS, amniocentesis, microarray testing, Fragile X, and spinal muscular atrophy screening
- Validated questionnaire to assess genetic risk in all pregnant women
- Screening high risk ethnic groups for hemoglobinopathies
- Screening for aneuploidy with any of five screening strategies [first trimester (nuchal translucency, beta-HCG and PAPP-A), integrated, serum integrated, stepwise sequential, and contingency]
- Ultrasound for structural anomalies between 18 and 20 weeks gestation
- CVS or amniocentesis for a positive aneuploidy screen, maternal age >34, fetal structural anomalies, family history of inheritable chromosomal disorder or elevated risk of neural tube defect.
- Array CGH when major fetal congenital anomalies apparent on imaging, and karyotype is normal
- FISH testing only if karyotyping is not possible due a need for rapid turnaround for reasons of reproductive decision-making (i.e. at 22w4d gestation or beyond)
- Screening for Tay-Sachs carrier status in high risk populations. First step is hex A, and then additional DNA analysis in individuals with ambiguous Hex A test results, suspected variant form of TSD or suspected pseudodeficiency of Hex A
- Screening for cystic fibrosis carrier status once in a lifetime
- Screening for fragile X status in patients with a personal or family history of
 - fragile X tremor/ataxia syndrome
 - premature ovarian failure
 - unexplained early onset intellectual disability
 - fragile X intellectual disability
 - unexplained autism through the pregnant woman's maternal line
- Screening for spinal muscular atrophy once in a lifetime
- Screening those with Ashkenazi Jewish heritage for Canavan disease, familial dysautonomia, Tay-Sachs carrier status and cystic fibrosis carrier status.
- Expanded carrier screening only for those genetic conditions identified above

The following are recommended for coverage (*strong recommendation*):

CG – Prenatal Genetic Testing

- Cell free fetal DNA testing for evaluation of aneuploidy in women who have an elevated risk of a fetus with aneuploidy (maternal age >34, family history or elevated risk based on screening)

The following are recommended for coverage (*strong recommendation*):

Cell free fetal DNA testing for evaluation of aneuploidy in women who have an elevated risk of a fetus with aneuploidy (maternal age >34, family history or elevated risk based on screening).

The following are not recommended for coverage (*weak recommendation*):

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

Current Prioritized List Status

Line 1 Pregnancy

Fetal ultrasounds, genetic counseling, genetic screening tests, amniocentesis/ CVS, etc. are all included on Line. Cell free fetal DNA (CPT 81507) is proposed for addition to this line with 2014 CPT code review. Serum triple screen could be included on line 1 if billed with CPT 81510.

Specifically, the following CPT codes are found on line 1:

- a. 59000 Amniocentesis; diagnostic
- b. 59015 Chorionic villus sampling, any method
- c. 76811 Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation plus detailed fetal anatomic examination, transabdominal approach; single or first gestation
- d. 76812 each additional gestation
- e. 76813 Ultrasound, pregnant uterus, real time with image documentation, first trimester fetal nuchal translucency measurement, transabdominal or transvaginal approach; single or first gestation
- f. 76814 each additional gestation
- g. 81508-81511 Fetal congenital abnormalities, biochemical assays

Most other genetic testing CPT codes are on the Diagnostic List.

Non-prenatal genetic testing is governed by a diagnostic guideline and testing algorithm.

CG – Prenatal Genetic Testing

HERC Staff Recommendations:

- 1) Adopt the following new guideline:

DIAGNOSTIC GUIDELINE XXX PRENATAL GENETIC TESTING

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

- 1) Genetic counseling (CPT 96040, HPCPS S0265) for high risk women who have family history of inheritable disorder or carrier state, ultrasound abnormality, previous pregnancy with aneuploidy, or elevated risk of neural tube defect
- 2) Genetic counseling (CPT 96040, HPCPS S0265) prior to CVS, amniocentesis, microarray testing, Fragile X, and spinal muscular atrophy screening
- 3) Validated questionnaire to assess genetic risk in all pregnant women
- 4) Screening high risk ethnic groups for hemoglobinopathies (CPT 83020, 83021)
- 5) Screening for aneuploidy with any of five screening strategies [first trimester (nuchal translucency, beta-HCG and PAPP-A), integrated, serum integrated, stepwise sequential, and contingency] (CPT 76813, 76814, 81508-81511)
- 6) Cell free fetal DNA testing (CPT 81507) for evaluation of aneuploidy in women who have an elevated risk of a fetus with aneuploidy (maternal age >34, family history or elevated risk based on screening).
- 7) Ultrasound for structural anomalies between 18 and 20 weeks gestation (CPT 76811, 76812)
- 8) CVS or amniocentesis (CPT 5900, 59015) for a positive aneuploidy screen, maternal age >34, fetal structural anomalies, family history of inheritable chromosomal disorder or elevated risk of neural tube defect.
- 9) Array CGH (CPT 81228) when major fetal congenital anomalies apparent on imaging, and karyotype is normal
- 10) FISH testing (CPT 88271) only if karyotyping is not possible due a need for rapid turnaround for reasons of reproductive decision-making (i.e. at 22w4d gestation or beyond)
- 11) Screening for Tay-Sachs carrier status (CPT 81255) in high risk populations. First step is hex A, and then additional DNA analysis in individuals with ambiguous Hex A test results, suspected variant form of TSD or suspected pseudodeficiency of Hex A
- 12) Screening for cystic fibrosis carrier status once in a lifetime (CPT 81220-81224)
- 13) Screening for fragile X status (CPT 81243, 81244) in patients with a personal or family history of
 - a. fragile X tremor/ataxia syndrome
 - b. premature ovarian failure
 - c. unexplained early onset intellectual disability
 - d. fragile X intellectual disability
 - e. unexplained autism through the pregnant woman's maternal line
- 14) Screening for spinal muscular atrophy (CPT 81401) once in a lifetime
- 15) Screening those with Ashkenazi Jewish heritage for Canavan disease (CPT 81200), familial dysautonomia (CPT 81260), and Tay-Sachs carrier status (CPT 81255)

CG – Prenatal Genetic Testing

16) Expanded carrier screening only for those genetic conditions identified above

The following genetic screening tests are not covered:

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

HEALTH EVIDENCE REVIEW COMMISSION (HERC)
COVERAGE GUIDANCE: PRENATAL GENETIC TESTING

DRAFT for VbBS Meeting Materials 10/10/2013

HERC COVERAGE GUIDANCE

The following are recommended for coverage (*weak recommendation*):

- Genetic counseling for high risk women who have family history of inheritable disorder or carrier state, ultrasound abnormality, previous pregnancy with aneuploidy, or elevated risk of neural tube defect
- Genetic counseling prior to CVS, amniocentesis, microarray testing, Fragile X, and spinal muscular atrophy screening
- Validated questionnaire to assess genetic risk in all pregnant women
- Screening high risk ethnic groups for hemoglobinopathies
- Screening for aneuploidy with any of five screening strategies [first trimester (nuchal translucency, beta-HCG and PAPP-A), integrated, serum integrated, stepwise sequential, and contingency]
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 - fragile X tremor/ataxia syndrome
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 - unexplained autism through the pregnant woman's maternal line
- Screening for spinal muscular atrophy once in a lifetime
- Screening those with Ashkenazi Jewish heritage for Canavan disease, familial dysautonomia, Tay-Sachs carrier status and cystic fibrosis carrier status.
- Expanded carrier screening only for those genetic conditions identified above

The following are recommended for coverage (*strong recommendation*):

- Cell free fetal DNA testing for evaluation of aneuploidy in women who have an elevated risk of a fetus with aneuploidy (maternal age >34, family history or elevated risk based on screening)

The following are not recommended for coverage (*weak recommendation*):

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

Note: Definitions for strength of recommendation are provided in Appendix A GRADE Element Description

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Health Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

EVIDENCE SOURCE

Little, A., Vandegriff, S., Zoller, E., Pettinari, C., Mayer, M., Kriz, H., & King, V. (2013). *Prenatal genetic testing: Evidence and guideline summary of select tests and conditions* [Produced for the Medicaid Evidence-based Decisions (MED) Project]. Portland, OR: Center for Evidence-based Policy, Oregon Health and Science University.

Key Sources Cited in MED Report:

Akkerman, D., Cleland, L., Croft, G., Eskuchen, K., Heim, C., Levine, A., et al. (2012). *Routine prenatal care*. Bloomington, MN: Institute for Clinical Systems Improvement (ICSI). Retrieved August 2, 2012, from <https://www.icsi.org/asset/13n9y4/Prenatal-Interactive0712.pdf>

Department of Veterans Affairs, & Department of Defense. (2009). *VA/DoD clinical practice guideline for pregnancy management*. Washington, DC: Department of Veterans Affairs, Department of Defense. Retrieved June 19, 2012, from <http://www.healthquality.va.gov/pregnancy.asp>

National Collaborating Centre for Women's and Children's Health, & National Institute for Health and Clinical Excellence (NICE). (2008). *Antenatal care: Routine care for the healthy pregnant woman*. London: RCOG Press. Retrieved June 19, 2012, from <http://www.nice.org.uk/guidance/CG62>

Technology Evaluation Center (TEC): (April 2013). *Sequencing-Based Tests to Determine Fetal Trisomy 21 from Maternal Plasma DNA*. Retrieved September 20, 2013 from <http://www.bcbs.com/blueresources/tec/vols/27/sequencing-based-tests-to.html>

The summary of evidence in this document is derived directly from this evidence source, and portions are extracted verbatim.

SUMMARY OF EVIDENCE

Clinical Background

Genetic testing detects alterations in DNA or chromosomes. Human genetic testing requires laboratory analyses of DNA, which is isolated from biologic samples, including cells, blood, or amniotic fluid. Tests for more than 1,300 genetic conditions are available. Genetic tests can be used to diagnose, predict risk for a future disease, inform reproductive decision-making, and manage patient care. There are eight categories of genetic testing: diagnostic, predictive, pharmacogenomic, prenatal, carrier, preimplantation, newborn, and research testing. This guidance document will focus only on recommendations for prenatal, carrier and diagnostic genetic testing. Prenatal testing is used to identify a fetus's genes or chromosomes before birth and is offered during pregnancy based on the risk that the baby will have a genetic or chromosomal disorder. Carrier testing is used to identify people who carry one copy of a gene mutation, which can cause a genetic disorder if two copies are present. Carrier testing is primarily offered to those with a family history of a specific genetic disorder and high-risk ethnic groups. Diagnostic testing is used to identify a specific genetic or chromosomal condition, and to confirm a diagnosis when a particular condition is suspected.

Evidence Review

General Prenatal Testing

A search of guideline databases (MED core sources plus the American College of Medical Genetics and the Canadian College of Medical Geneticists) was conducted from 2008 to present and identified 28 guidelines, three of which addressed general prenatal care [NICE (2008), VA/DoD (2009), and ICSI (Akkerman [ICSI] 2012)]. All three were rated good quality and provided detailed guidance on general prenatal care, with specific recommendations related to genetic testing. All three recommend screening measures and testing indications for aneuploidy screening, general risk assessment and screening options for hemoglobinopathies, cystic fibrosis, and structural

abnormalities. One guideline addresses screening for Tay-Sachs disease. Recommendations from all three guidelines are consistent with a few exceptions:

- Ultrasound screening for structural anomalies is recommended only by NICE (optional for ICSI and VA/DoD); and
- Method of aneuploidy screening is specified only by NICE, which recommends the combined test in the first trimester as the most desirable strategy. The other two guidelines do not recommend one strategy for testing over another.
- NICE does not recommend carrier testing for cystic fibrosis

Prenatal genetic testing recommendations are summarized and compared in the table below:

Indication/Test	NICE (2008)	VA/DoD (2009)	ICSI (2012)
Genetic risk assessment	Validated questionnaire	Validated questionnaire	Validated questionnaire
Hemoglobinopathies	Screen all high-risk ethnic groups ¹ , complete blood count test, hemoglobin electrophoresis test.	Screen all high-risk ethnic groups, complete blood count test, hemoglobin electrophoresis test.	Screen all high-risk ethnic groups, complete blood count test, hemoglobin electrophoresis test.
Cystic fibrosis	Addressed in separate guideline – testing not recommended	Carrier test/counseling	Carrier test/counseling
Tay-Sachs disease	-	-	Leukocyte hexosaminidase A test for high-risk ethnic groups
Aneuploidy screening	First choice (for women who enter care in the first trimester): nuchal translucency (NT), beta-human chorionic gonadotropin (beta-hCG), and pregnancy-associated plasma protein A (PAPP-A) (11	Any of the following, based on the woman's choice: First- or second-trimester serum marker assessment, first-trimester NT measurement, basic and comprehensive second-trimester ultrasound assessment, first-trimester chorionic villus sampling and	Any of four screening strategies (integrated, serum integrated, stepwise sequential, and contingency) ⁴ .

¹ Women of African, Southeast Asian (excluding Japanese and Korean) or Mediterranean descent

⁴ See below for description of these screening strategies

Indication/Test	NICE (2008)	VA/DoD (2009)	ICSI (2012)
	weeks 0 days and 13 weeks 6 days); Second choice (for women who present later in the pregnancy): triple² or quadruple³ test (15 weeks 0 days and 20 weeks 0 days).	second-trimester amniocentesis. If first trimester screening is elected: second-trimester serum AFP screening and/or US should be offered to screen for open neural tube defects. For second trimester serum screening: Quad Marker Screen should be used rather than the Triple Marker Screen.	
Structural abnormality screen	Between 18 weeks 0 days and 20 weeks 6 days	Optional - only as needed	Optional 18-20 weeks
Chorionic Villus Sampling (CVS) or Amniocentesis	Provide information at first visit Offer if positive aneuploidy screening (details not provided) Offer if both parents are sickle cell or thalassemia carriers	Maternal request Offer CVS in first trimester if: • Age over 34 • Abnormal first trimester screen (risk estimate similar to that of 35 year old woman [1/270]) • Fetal structural anomalies • Positive family history for metabolic/genetic disorder Offer amniocentesis if: • Abnormal first or second trimester screen (risk estimate similar to that of 35 year old woman [1/270])	Three different screening algorithms provided, with no recommendation for which to use Perform risk assessment using first trimester strategy (nuchal translucency, serum PAPP-A, patient age) and/or second trimester strategy (triple or quad screen) High, intermediate and low risk not specified, but examples given (1/50, 1/200) CVS or amniocentesis offered if screening

² Serum AFP, estriol and beta-hCG

³ Serum AFP, estriol, beta-hCG and dimeric inhibin A

Indication/Test	NICE (2008)	VA/DoD (2009)	ICSI (2012)
		- Fetal ultrasound anomalies - Positive family history for metabolic/genetic disorder - Elevated risk of open neural tube defect	suggests “high risk”, depending on gestational age

Screening strategies as outlined in the ICSI guideline:

- Integrated screening: The patient is scanned for nuchal translucency determination and has a serum PAPP-A analysis performed between 10 and 13 weeks. The results of these tests are held, and the patient then has a quadruple screen test performed between 15 and 19 weeks. At that time, the results of all the studies, combined with risk assessment due to the patient's age, are used to present a single-risk figure. Patients at “high risk” are offered amniocentesis (Trisomy 21 detection rate = 94-96%). “High risk” is not defined, but qualified with the following language: “Each clinician/health care organization will establish cutoff values for low and high risk based on laboratory and patient particulars. One system used is 1 in 200 as the cutoff.”
- Serum integrated screening: A variation in which the first-trimester PAPP-A test result is combined with a second-trimester quad test to provide a single-risk figure is called a serum integrated screening. (Trisomy 21 detection rate = 85-88%).
- Stepwise sequential screening: The patient is scanned for nuchal translucency determination and has a serum PAPP-A analysis performed between 10 and 13 weeks. The results of these studies are combined with the patient's age-associated risk, and the patient is given a risk assessment for aneuploidy. The patient may choose at this time to undergo invasive testing (i.e., CVS), or a triple or quad screen at 15-19 weeks. If the patient has the second-trimester test, a new risk is assessed based on the results of her age and both the first- and second-trimester screening test results (Trisomy 21 detection rate = 95%). Those at “high risk” are offered amniocentesis. “High risk” is not defined, but qualified with the following language: “Each clinician/health care organization will establish cutoff values for low and high risk based on laboratory and patient particulars. One system used is 1 in 200 as the cutoff.”
- Contingency screening: The patient has the same first-trimester study described for the stepwise sequential test and is told the results. If the results are above an arbitrary cutoff, such as 1 in 50, she is offered CVS. If her results are below another

arbitrary cutoff, such as 1 in 1,000, she is advised that no further testing is necessary. If the patient's risk falls between these two cutoffs, she is offered a quad screen after 15 weeks, and a new risk assessment is determined as in the stepwise sequential test (Trisomy 21 detection rate = 88-94%). Those at “high risk” are offered amniocentesis. “High risk” is not defined, but qualified with the following language: “Each clinician/health care organization will establish cutoff values for low and high risk based on laboratory and patient particulars. One system used is 1 in 200 as the cutoff.”

Genetic Counseling

The NICE guideline does not address women with a family history of a genetic disorder, or specify indications for genetic counseling. The ICSI guideline does not specify indications for genetic counseling with the exception of women with a family history of Fragile X disease or mental retardation. The VA/DoD guideline recommends that genetic counseling be provided to any woman identified as high risk, defined as advanced maternal age, personal or family history of genetic disorder or positive screening test result.

Specific Prenatal Tests or Testing Techniques

A search of clinical evidence sources and guideline databases (MED core sources plus the American College of Medical Genetics and the Canadian College of Medical Geneticists) was conducted from 2003 to present (2008 to present for guidelines). Twenty-four evidence reviews and 28 guidelines were identified, all of which addressed specific genetic tests with the exception of the three general prenatal guidelines discussed above. No quality assessment of the guidelines was done.

Fetal Aneuploidy

Prenatal diagnosis of aneuploidy is suggested by use of maternal screening tests, as reviewed above. All such tests have less than perfect sensitivity and require definitive fetal testing if abnormal. Definitive testing for aneuploidy has historically been an invasive procedure, accomplished by amniocentesis or chorionic villus sampling. However, recently, other methods to detect common aneuploidies have been developed. Four of these are outlined below.

Quantitative Fluorescent-Polymerase Chain Reaction (QF-PCR)

This is a PCR-based technique that consists of amplifying polymorphic markers located on the chromosomes of interest (generally, chromosomes 13, 18, 21, X or Y) to determine the number of copies of those chromosomes present per cell. The advantages of QF-PCR are that it requires a small sample (culture of amniocytes is not required), and the procedure can be automated, providing a rapid turnaround time at a lower cost than conventional cytogenetics. Moreover, diagnostic testing with QF-PCR

eliminates the unexpected or incidental identification of rare chromosomal abnormalities of uncertain significance.

No evidence was identified that addressed this test. One guideline was identified, produced by collaboration of the Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC) joined with the Prenatal Diagnosis Committee of the Canadian College of Medical Genetics in 2011. They state that *“QF-PCR is a reliable method to detect trisomies and should replace conventional cytogenetic analysis whenever prenatal testing is performed solely because of an increased risk of aneuploidy in chromosomes 13, 18, 21, X or Y.”*

Microarray Testing

Microarray testing generally refers to array comparative genomic hybridization (array CGH), which uses a high resolution analysis of the genome to identify losses or duplications to the chromosome. These deletions and duplications are referred to as copy number variations (CNV). Conventional chromosome analysis using G-banding will detect chromosome anomalies such as trisomies 21, 18 and 13, and monosomy X, along with many structural rearrangements. However, it only detects anomalies to a resolution of 5-10 Mb (million base-pairs). Array CGH, on the other hand, is capable of detecting changes to a resolution of 1 kb (thousand base-pairs) which is smaller than the average gene, and customized arrays designed for prenatal diagnosis have been developed.

One of the challenges of the application of CGH microarrays in the clinical setting is determining whether a copy number imbalance is *de novo* and likely to be causative, or inherited and likely to be benign. Copy number variants (CNVs) are categorized into those that are likely to be ‘benign,’ those that are likely to be ‘pathogenic’ and those of ‘unknown clinical significance.’ Copy number variants that overlap critical regions of established microdeletion or microduplication syndromes are likely to be pathogenic, but there is a high incidence of CNVs in the normal population, making the significance of many CNVs uncertain. Although array CGH has higher resolution to detect these small chromosomal changes, it cannot detect balanced rearrangements such as transformations or inversions. Identifying CNVs of uncertain significance increases parental anxiety and makes genetic counseling more challenging.

For microarray testing, a systematic review found that array CGH detected 3.6% additional genomic imbalances when conventional karyotyping was normal, regardless of the reason for performing the study, and increased to 5.2% when the indication for performing the study was a structural malformation on ultrasound. Three guidelines were identified that address array CGH and make similar recommendations. None of the three recommend array CGH testing for pregnancies at low risk of chromosome

abnormalities. All three recommend this technology when fetal structural abnormalities are identified on ultrasound or MRI, although one recommends that it be utilized only if conventional karyotyping is normal. All three also recommend genetic counseling for all patients utilizing the technology.

Fluorescent In Situ Hybridization (FISH) DNA Testing

This is a rapid technique that relies on fluorescent in situ hybridization (FISH) that provides results in one to two days, in which fluorescently labeled DNA probes are bound to fetal cell DNA in a highly selective manner, allowing detection of changes in the number of specific chromosomes by detecting the fluorescence. To detect the most common disorders involving chromosome number, fluorescent probes are used that bind to chromosomes 13, 18, 21, X, and Y. However, this technique fails to detect many other potentially harmful changes in chromosomes that can be detected by conventional karyotyping, such as certain rearrangements of segments of chromosomes.

One TA was identified that addressed this topic. It included three large studies that compared results obtained with FISH with those obtained with conventional karyotyping. Results suggest that FISH is a highly accurate test for detection of most, but not all, potentially harmful chromosomal abnormalities, with sensitivity and specificity for detection of the targeted abnormalities exceeded 99.5%. However, it is unable to detect 7% to 11% of potentially harmful chromosomal disorders that can be detected by karyotyping.

Cell Free Fetal DNA Testing

Fetal DNA circulates in maternal blood during pregnancy, making up approximately 10% of all circulating DNA. Recently, cell free DNA testing has been used to identify common aneuploidies. These tests utilize maternal blood, from which fetal DNA can be isolated as early as ten weeks gestation. Repeated parallel sequencing can then detect an excess of the chromosome of interest of fetal origin, indicating the specific aneuploidy.

No evidence was identified in the MED report. One guideline recommends that cell free DNA testing be offered to patients at increased risk of aneuploidy⁵. They recommend that it NOT be a part of routine prenatal laboratory measurements or be offered to low risk women.

The Blue Cross TEC Assessment Program analyzed this technology and identified eight studies that reported on the performance of cff-DNA for trisomy 21 screening in singleton high-risk pregnancies. They found that cff-DNA testing reduced the number of

⁵ Maternal age ≥ 35 , suggestive US findings, history of prior trisomy pregnancy, positive aneuploidy screen or parental balanced robertsonian translocation with increased risk for fetal trisomy 13 or 21
Coverage Guidance: Prenatal Genetic Testing

invasive confirmatory procedures needed and consequent associated miscarriages, while improving the number of detected cases of trisomy 21, compared to standard screening procedures in high-risk populations of pregnant women. They therefore concluded that ccf-DNA meets the TEC criteria.

Tay-Sachs Disease

Tay-Sachs disease is an autosomal recessive lysosomal storage disease caused by a deficient activity of the enzyme hexosaminidase A (Hex A). It occurs in 1 in 2500 children of Ashkenazi Jewish parents, and is most common among people who are Ashkenazi Jewish, French-Canadian, or Cajun. Hex A activity can be measured in serum, white blood cells, or fetal trophoblastic cells, and is used as the initial screening test for TSD mutation carriers. However, in some cases, the enzyme test may not be diagnostic, and DNA analysis may be necessary to clarify ambiguous enzyme test results or to diagnose variant forms of the disease.

One review that included four studies and a retrospective analysis found that hexoaminidase A testing is accurate and impacts both pre and post-conception reproductive decision making. The review concludes that the evidence is sufficient to support the use of screening by Hex A enzyme testing individuals at high risk (Ashkenazi Jewish, French-Canadian or with positive family history) or partners of known carriers. It is also sufficient to support additional DNA analysis in individuals with ambiguous Hex A test results, suspected variant form of TSD or suspected pseudodeficiency of Hex A. The one guideline identified recommends that Hex A screening be offered to all pregnant Jewish patients if they or their partners have not yet been tested.

Cystic Fibrosis

Cystic Fibrosis is an autosomal recessive disease of the exocrine glands that is characterized by early onset of severe intestinal malabsorption, failure to thrive and recurrent chest infections and pneumonia which, if untreated, leads to death from malnutrition and respiratory failure in infancy or early childhood. The identification of the gene responsible for CF, *CFTR*, and its major mutations, allow for the identification of couples at risk who can be offered genetic counseling and prenatal CF diagnosis, and who can use the information to inform reproductive decision-making. Since heterozygotes are asymptomatic, carrier status assumes clinical significance only in the context of reproduction.

A review of 10 population-based studies found carrier testing was 80% to 96% sensitive in Caucasians and 58% to 76% sensitive in Hispanics. Uptake rates for testing ranged from 68% to 95%. The evidence was sufficient to support the use of CF carrier screening if results will be used to guide decisions regarding childbearing or need for fetal diagnosis. A second review reported analytic sensitivity of 97.9% and analytic

specificity of 99.4%, but clinical sensitivity of only 75%. Uptake rates in this review were reported as 85% to 100%, and of the affected fetuses identified, 83% were terminated. Four guidelines were identified, three of them addressing general prenatal care and offering differing recommendations. Two recommend that CF carrier screening be offered to all couples who desire it and have not been previously screened, while the third does not recommend screening. The one guideline that addressed CF carrier screening outside the context of general prenatal care recommends carrier testing in individuals and their partners with a positive family history, and prenatal diagnosis for pregnancies at 25% or greater risk of CF, and those with an echogenic bowel identified in the fetus.

Fragile X Syndrome

Fragile X Syndrome is the most common inherited cause of mental retardation, and results from a dynamic mutation (those that can change as they are passed down to future generations). In normal individuals there are six to 50 repeats of the CGG sequence of DNA at the Fragile X site. When the number of repeats ranges between 50 and 200, this is known as a premutation (PM); more than 200 repeats is considered a full mutation (FM). Full mutations inactivate the gene resulting in the Fragile X phenotype in all males (who only have one copy of the gene) and a proportion of females (all will be carriers, some will have the phenotype). A female with a PM or a FM may pass on a larger mutation than her own, resulting in offspring affected by Fragile X syndrome. Meanwhile, men with a PM may pass this onto their daughters, who will be of normal intellect, but may pass a larger mutation onto their offspring. The larger the size of the premutation repeat, the more likely is the expansion to a full mutation.

A systematic review that compared antenatal screening of low risk versus high risk women identified no studies, while a health technology assessment that compared different screening strategies for Fragile X syndrome found that population-based prenatal screening is more efficacious but significantly more costly than active cascade screening⁶, with the incremental cost per Fragile X birth avoided being £8494 for active cascade screening and £284,779 for population-based screening. Three guidelines address testing for Fragile X and offer generally consistent recommendations. These include genetic counseling of all testing recipients, carrier screening of women with a positive personal or family history of fragile X-rated disorders, unexplained mental retardation or premature ovarian failure, and prenatal fetal DNA testing for known carriers.

Heritable Thrombophilia

Pregnancy is associated with an increased risk of venous thromboembolism, as are inherited thrombophilias. However, it is controversial whether there is an association

⁶ Testing relatives of Fragile X patients to determine carrier status

between inherited thrombophilias and adverse pregnancy outcomes such as fetal loss, preeclampsia, fetal growth restriction, and placental abruption. This possible association has resulted in increased screening for thrombophilias in pregnancy, although there has been no confirmation of treatment benefits.

For heritable thrombophilia, one systematic review resulted in a recommendation to not screen for heritable thrombophilia in any group. One guideline was identified that addresses inherited thrombophilias in pregnancy. Regarding screening, it recommends against testing in women with recurrent fetal loss or placental abruption, and finds insufficient evidence to support testing in women with previous preeclampsia or intrauterine growth restriction. For women diagnosed with hereditary thrombophilia and/or with a history of thromboembolism, the guideline provides specific recommendations for which tests to perform, and for antepartum and postpartum management.

Fetal Skeletal Dysplasia

Skeletal dysplasias may present in the prenatal period when demonstrated by abnormalities on ultrasound. Differentiating these disorders in the prenatal period can be useful to distinguish known lethal disorders from nonlethal disorders and to assist with determining post-delivery management plans. One guideline was identified that provides specific recommendations for management based on abnormal findings of a second trimester ultrasound. Those recommendations include a determination of lethality based on ultrasound measurements, and molecular testing of pregnancies identified as at-risk for skeletal dysplasias.

Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disease that results from degeneration of spinal cord motor neurons leading to atrophy of skeletal muscle and overall weakness. The incidence of SMA is approximately 1 in 10,000 live births, and it is reported to be the leading genetic cause of infant death, although milder forms allow survival into adulthood. Two guidelines were identified, with conflicting recommendations. One did not recommend screening for SMA in the general population, but did recommend carrier screening for those with a family history of SMA-like disease. The other recommends that carrier testing be offered to all couples.

Ethnicities with Elevated Genetic Risk

For ethnicities at increased genetic risk, two guidelines were identified with conflicting recommendations for screening those of Ashkenazi Jewish descent. Both recommend carrier screening for Tay-Sachs disease, Canavan disease, cystic fibrosis, and familial dysautonomia. One also recommends screening for Fanconi anemia, Bloom syndrome, Mucopolysaccharidosis IV, Niemann-Pick type A and Gaucher disease type I, while the other only recommends that patient education materials be made available to patients concerning

these conditions. Both groups also recommend carrier screening for Tay Sachs disease for individuals of French Canadian and Cajun origin.

Genetic Counseling

All three guidelines pertaining to microarray testing recommend that it be accompanied by genetic counseling. Guidelines addressing other specific genetic tests recommend genetic counseling be provided in the following situations: a positive cell free fetal DNA testing result, any cystic fibrosis carrier, women with risk factors for Fragile X or who request testing for Fragile X and women with a family history of, or who request testing for, spinal muscular atrophy.

Evidence Summary

Evidence-based guidelines for routine prenatal care are generally consistent regarding their recommendations related to genetic testing, recommending aneuploidy screening and screening options for hemoglobinopathies, cystic fibrosis, and structural abnormalities. Recommendations on specific tests were generally not based on trusted sources due to lack of availability of evidence and are derived from guidelines of variable quality.

There are four options available for aneuploidy testing in addition to the traditional method of karyotyping, which requires an invasive procedure (amniocentesis or chorionic villus sampling) and amniocyte culture. Three of the four do not require the culture of amniocytes, allowing a more rapid turnaround time, but at the expense of a less accurate or complete diagnosis. They include QF-PCR, FISH testing and cell free fetal DNA testing. No evidence was identified for QF-PCR or cell free DNA testing, while evidence for FISH suggests that it is a highly accurate test for detection of most potentially harmful chromosomal abnormalities, although it is unable to detect 7% to 11% of chromosomal disorders that can be detected by karyotyping.

The fourth method, array CGH testing, is limited by difficulty determining whether a copy number imbalance is likely to be causative or benign, as well as the inability to detect balanced rearrangements. Evidence suggests that array CGH detects approximately 5% additional genomic imbalances when conventional karyotyping is normal, if the indication for performing the study is a structural malformation on ultrasound. None of the three identified guidelines recommend array CGH testing for pregnancies at low risk of chromosome abnormalities, but all recommend it when fetal structural abnormalities are identified.

For Tay-Sachs disease, the evidence is sufficient to support the use of screening by Hex A enzyme testing for individuals at high risk (Ashkenazi Jewish, French-Canadian or with positive family history) or partners of known carriers. It is also sufficient to

support additional DNA analysis in individuals with ambiguous Hex A test results, suspected variant form of TSD or suspected pseudodeficiency of Hex A.

For cystic fibrosis, the evidence is sufficient to support the use of CF carrier screening if results will be used to inform decisions regarding childbearing or need for fetal diagnosis.

For Fragile X Syndrome, three guidelines recommend carrier screening of women with a positive personal or family history of Fragile X-rated disorders, unexplained mental retardation or premature ovarian failure, and prenatal fetal DNA testing for known carriers.

For heritable thrombophilia, evidence supports and one guideline recommends not screening for heritable thrombophilia in any group.

For fetal skeletal dysplasia, one guideline recommends determining lethality based on ultrasound measurements and molecular testing of at-risk pregnancies.

For spinal muscular atrophy, two guidelines had conflicting recommendations, with one recommending carrier screening to all couples and the other recommending only for those with a family history of SMA-like disease.

For ethnicities at increased genetic risk, two guidelines recommend screening those of Ashkenazi Jewish descent for Tay-Sachs disease, Canavan disease, cystic fibrosis, and familial dysautonomia, but disagree about screening for four additional conditions.

GRADE-INFORMED FRAMEWORK

The HERC develops recommendations by using the concepts of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for carrying out the steps involved in developing recommendations. There are four elements that determine the strength of a recommendation, as listed in the table below. The HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Balance between desirable and undesirable effects, and quality of evidence, are derived from the evidence presented in this document, while estimated relative costs, values and preferences are assessments of the HERC members.

Indication	Balance between desirable and undesirable effects	Quality of evidence	Resource Allocation	Values and preferences	Coverage Recommendation
Use a validated questionnaire to assess genetic risk in all pregnant women	Likely beneficial without known risks	Low	Limited	Limited variability	Administration of a validated questionnaire to assess genetic risk is recommended for coverage <i>(weak recommendation)</i>
Screen high-risk ethnic groups for hemoglobinopathies	Likely beneficial, minimal risks	High	Limited	Limited variability	Screening high risk ethnic groups for hemoglobinopathies is recommended for coverage <i>(weak recommendation)</i>
Aneuploidy screening in first or second trimester	Likely beneficial, minimal risks	Moderate	Moderate	Moderate variability	Screening for aneuploidy with any of the four screening strategies (integrated, serum integrated, stepwise sequential, and contingency) is recommended for coverage <i>(weak recommendation)</i> Serum triple screen is not recommended for coverage <i>(weak recommendation)</i>

Indication	Balance between desirable and undesirable effects	Quality of evidence	Resource Allocation	Values and preferences	Coverage Recommendation
Perform an US for structural anomaly screen at 18-20 weeks	Possibly beneficial, minimal risks	Low	Moderate	Limited variability	Ultrasound for structural anomalies between 18-20 weeks gestation is recommended for coverage (<i>weak recommendation</i>)
Offer CVS or amnio for + aneuploidy screen, maternal age > 34, fetal structural anomalies, + FH, elevated risk of neural tube defect or maternal request	Mixed – Moderate benefit depending on patient preferences, small risk (pregnancy loss 1/300-500)	Mixed	High	High variability	CVS and amniocentesis are recommended for coverage for a positive aneuploidy screen, maternal age >34, fetal structural anomalies, positive family history, elevated risk of neural tube defect, or maternal request (<i>weak recommendation</i>) Genetic counseling is recommended for coverage prior to CVS/amniocentesis (<i>weak recommendation</i>)
Aneuploidy testing with QF-PCR	Similar risk to karyotyping, may be more beneficial when rapid turnaround is required	None	Moderate	High variability	<i>Test not available in the US – no recommendation made</i>
Array CGH testing when karyotype normal and structural anomaly on US	Similar risk to karyotyping, similar benefits (detection of more chromosomal anomalies, but also more anomalies of no clinical significance, resulting in increased maternal anxiety)	Low	Moderate	Limited variability (because anomalies already identified)	Recommended for coverage when major fetal congenital anomalies apparent on imaging and karyotype is normal (<i>weak recommendation</i>)

Indication	Balance between desirable and undesirable effects	Quality of evidence	Resource Allocation	Values and preferences	Coverage Recommendation
Aneuploidy testing with FISH	Similar risk to karyotyping, may be more beneficial when rapid turnaround is required	Moderate	High	High variability (because use for pregnancy decision making only)	Karyotyping is first line test. If a rapid turnaround (i.e. at 22w4d or beyond) is required for reproductive decision-making, FISH is recommended for coverage (<i>weak recommendation</i>)
Cell free fetal DNA testing	High level of accuracy (98% detection rate with false positive < 0.5%). Less risk than karyotyping but less information provided (current tests only identify trisomy 13, 18 and 21)	None	High	Moderate variability (many women would choose a noninvasive highly accurate test)	Cell free fetal DNA testing is not recommended for coverage (<i>weak recommendation</i>)
Screening for Tay-Sachs carrier status using Hex A in high risk populations ⁷	Benefits exceed harms	Moderate	Low	Limited variability (most would choose to terminate)	Screening for Tay-Sachs carrier status in high risk populations is recommended for coverage. First step is Hex A, and then additional DNA analysis in individuals with ambiguous Hex A test results, suspected variant form of TSD or suspected pseudodeficiency of Hex A (<i>weak recommendation</i>)

⁷ Ashkenazi Jewish, French Canadian and Cajun
Coverage Guidance: Prenatal Genetic Testing
DRAFT for VbBS Meeting Materials 10/10/2013

Indication	Balance between desirable and undesirable effects	Quality of evidence	Resource Allocation	Values and preferences	Coverage Recommendation
Screening for CF carrier status	Potential benefit, minimal harm	Moderate	Moderate	Moderate variability	Screening for cystic fibrosis status is recommended for coverage once in a lifetime (<i>weak recommendation</i>)
Screening for fragile X carrier status in women with +FH or risk factors ⁸	Small benefit, depending on values of parents, minimal harm	Low	Moderate	Moderate variability	Screening for fragile X status in patients with a personal or family history of • fragile X tremor/ataxia syndrome • premature ovarian failure • unexplained early onset intellectual disability • fragile X intellectual disability • unexplained autism through the pregnant woman's maternal line adult
Screening for thrombophilia	No definite benefit, possible harm if prophylactic treatment undertaken (bleeding risks from anticoagulation)	Low	Moderate (if treatment undertaken)	Limited	Screening for thrombophilia is not recommended for coverage for recurrent pregnancy loss <u>or in the general population</u> (<i>weak recommendation</i>)
Fetal genetic analysis of fetuses at risk for fetal skeletal dysplasia based on US	Mixed – Moderate benefit depending on patient preferences, small risk	Low	Moderate (cascade of testing)	Moderate variability	<i>No recommendation made</i>

⁸ Personal or family history of fragile X tremor/ataxia syndrome, unexplained mental retardation, autism or premature ovarian failure (before age 40)

Indication	Balance between desirable and undesirable effects	Quality of evidence	Resource Allocation	Values and preferences	Coverage Recommendation
Spinal muscular atrophy carrier screening	Small benefit, depending on values of parents, minimal harm	None	Low	Moderate variability	Screening for spinal muscular atrophy is recommended for coverage once in a lifetime (<i>weak recommendation</i>)
Screening of Ashkenazi Jewish population for specific genetic diseases	Likely beneficial, minimal risks	Low	Moderate	Moderate variability	Screening is recommended for coverage for those of Ashkenazi Jewish heritage for Tay-Sachs disease, Canavan disease, cystic fibrosis, and familial dysautonomia (<i>weak recommendation</i>)
Expanded carrier screening	Components likely beneficial, however, there is a risk of cascade testing, clinically unimportant results	None	Moderate. There is a cascade of testing. However, compared to individual diagnostic tests, this type of testing is much less expensive	High variability	Coverage is recommended for expanded carrier screening only for those genetic conditions previously identified with enough evidence or guidelines to support a recommendation for coverage (<i>weak recommendation</i>) Coverage is not recommended for an unlimited variety of tests offered as part of expanded carrier screening (<i>weak recommendation</i>)
Genetic counseling	Beneficial in greater understanding of risks and benefits	Moderate	Cost of appointment may be balanced by optimizing appropriate test utilization	Low variability (most women would choose to see a genetic counselor)	Pretest genetic counseling is recommended for coverage prior to CVS, amniocentesis, Fragile X, microarray, and spinal muscular atrophy screening (<i>weak recommendation</i>)

Note: GRADE framework elements are described in Appendix A

POLICY LANDSCAPE

There were no quality measures pertaining to prenatal genetic testing identified when searching the [National Quality Measures Clearinghouse](#).

COMMITTEE DELIBERATIONS –EBGS

In its review of this topic at its meetings April 4, June 6 and September 7, 2013, EbGS reviewed the initial draft coverage guidance and made the following decisions (some decisions from early meetings were later reversed; the final decisions are reflected here):

- Recommend coverage for CVS/Amniocentesis for the indication of ‘on maternal request’ as a weak recommendation.
- Make no recommendation on QF-PCR as the test is not available in the United States.
- In Array CGH testing when the karyotype is normal and there is a structural anomaly on ultrasound, the subcommittee decided to remove the recommendation for genetic counseling, as counseling would already have occurred before the CVS/amniocentesis. For Array CGH with stillbirth at >20 weeks gestation, the subcommittee decided to strike the recommendation, as none of the evidence reviewed supports its use in improving future pregnancy outcomes.
- Decided to recommend coverage for Cell Free Fetal DNA testing for high risk pregnancies based on new evidence from trusted sources which was submitted during public comment.
- Change the recommendation for thrombophilia screening to clarify that the recommendation applies to women with a history of recurrent pregnancy loss and that using this test for screening is not recommended.
- Recommend coverage for spinal muscular atrophy only once in a lifetime with pretest genetic counseling.
- Recommend coverage for carrier screening in the Ashkenazi Jewish population for only four conditions rather than eight.

COMMITTEE DELIBERATIONS – VBBS

Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

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Appendix A. GRADE Element Descriptions

Element	Description
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Resource allocation	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted

Strong recommendation

In Favor: The subcommittee is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Against: The subcommittee is confident that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Weak recommendation

In Favor: the subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Against: the subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Quality of evidence across studies for the treatment/outcome

High = Further research is very unlikely to change our confidence in the estimate of effect.

Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low = Any estimate of effect is very uncertain.

Appendix B. Applicable Codes

CODES DESCRIPTION	
ICD-9 Diagnosis Codes	
V18.4	Family history of intellectual disabilities
V18.9	Family history of genetic disease carrier
V26.31	Testing of female for genetic disease carrier status
V26.32	Other genetic testing of female
V26.33	Genetic counseling
V26.34	Testing of male for genetic disease carrier status
V26.35	Encounter for testing of male partner of female with recurrent pregnancy loss
V26.39	Other genetic testing of male
V28.0	Antenatal screening for chromosomal anomalies by amniocentesis
V28.1	Antenatal screening for raised alpha-fetoprotein levels in amniotic fluid
V28.2	Other antenatal screening based on amniocentesis
V28.3	Encounter for routine screening for malformation using ultrasonics
V28.89	Other specified antenatal screening
V28.9	Unspecified antenatal screening
ICD-9 Volume 3 (Procedure Codes)	
None	
CPT Codes	
81161	DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed
81200	<i>ASPA (aspartoacylase)</i> (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X)
81205	<i>BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide)</i> (eg, Maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X)
81209	<i>BLM (Bloom syndrome, RecQ helicase-like)</i> (eg, Bloom syndrome) gene analysis, 2281del6ins7 variant)
81220	<i>CFTR (cystic fibrosis transmembrane conductance regulator)</i> (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
81221	known familial variants
81222	duplication/deletion variants
81223	full gene sequence
81224	intron 8 poly-t analysis (eg, male infertility)
81225	<i>CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19)</i> (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)
81226	<i>CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6)</i> (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
81227	<i>CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9)</i> (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)
81228	Cytrogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (eg, Bacterial Artificial Chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)
81229	interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities

CODES	DESCRIPTION
81240	<i>F2 (prothrombin, coagulation factor II)</i> (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant
81241	<i>F5 (coagulation Factor V)</i> (eg, hereditary hypercoagulability) gene analysis, Leiden variant
81242	<i>FANCC (Fanconi anemia, complementation group C)</i> (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A>T)
81243	<i>FMR1 (Fragile X mental retardation 1)</i> (eg, fragile X mental retardation) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81244	characterization of alleles (eg, expanded size and methylation status)
81250	<i>G6PC (glucose-6-phosphatase, catalytic subunit)</i> (eg, Glycogen storage disease, Type 1a, von Gierke disease) gene analysis, common variants (eg, R83C, Q347X)
81251	<i>GBA (glucosidase, beta, acid)</i> (eg, Gaucher disease) gene analysis, common variants (eg, N370S, 84GG, L444P, IVS2+1G>A)
81252	<i>GJB2 (gap junction protein, beta 2, 26kDa, connexin 26)</i> (eg, nonsyndromic hearing loss) gene analysis; full gene sequence
81253	known familial variants
81254	<i>GJB6 (gap junction protein, beta 6, 30kDa, connexin 30)</i> (eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])
81255	<i>HEXA (hexosaminidase A [alpha polypeptide])</i> (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G>C, G269S)
81256	<i>HFE (hemochromatosis)</i> (eg, hereditary hemochromatosis) (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D)
81257	<i>HBA1/HBA2 (alpha globin 1 and alphaglobin 2)</i> (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, for common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring)
81260	<i>IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein)</i> (eg, familial dysautonomia) gene analysis, common variants (eg, 2507+6T>C, R696P)
81280	Long QT syndrome gene analyses (eg, <i>KCNQ1</i> , <i>KCNH2</i> , <i>SCN5A</i> , <i>KCNE1</i> , <i>KCNE2</i> , <i>KCNJ2</i> , <i>CACNA1C</i> , <i>CAV3</i> , <i>SCN4B</i> , <i>AKAP</i> , <i>SNTA1</i> , and <i>ANK2</i>); full sequence analysis
81281	known familial sequence variant
81282	duplication/deletion variants
81290	<i>MCOLN1 (mucolipin 1)</i> (eg, Mucolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A>G, del6.4kb)
81291	<i>MTHFR (5,10-methylenetetrahydrofolate reductase)</i> (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
81292	<i>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2)</i> (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81293	known familial variants
81294	duplication/deletion variants
81295	<i>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1)</i> (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81296	known familial variants
81297	duplication/deletion variants

CODES	DESCRIPTION
81298	<i>MSH6 (mutS homolog 6 {E. coli})</i> (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81299	known familial variants
81300	duplication/deletion variants
81301	Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
81302	<i>MECP2 (methyl CpG binding protein 2)</i> (eg, Rett syndrome) gene analysis; full sequence analysis
81303	known familial variant
81304	duplication/deletion variants
81317	<i>PMS2 (postmeiotic segregation increased 2 [S. cerevisiae])</i> (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81318	known familial variants
81319	duplication/deletion variants
81321	<i>PTEN (phosphatase and tensin homolog)</i> (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
81322	known familial variant
81323	duplication/deletion variants
81324	<i>PMP22 (peripheral myelin protein 22)</i> (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
81325	full sequence analysis
81326	known familial variant
81330	<i>SMPD1 (sphingomyelin phosphodiesterase 1, acid lysosomal)</i> (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)
81331	<i>SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A)</i> (eg, Prader-Willi syndrome and/or Angelman syndrome), methylation analysis
81332	<i>SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1-antitrypsin, member 1)</i> (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z)
88267	Chromosome analysis, amniotic fluid or chorionic villus, count 15 cells, 1 karyotype, with banding
88269	Chromosome analysis, in situ for amniotic fluid cells, count cells from 6-12 colonies, 1 karyotype, with banding
88271	Molecular cytogenetics; DNA probe, each (eg, FISH)
88272	chromosomal in situ hybridization, analyze 3-5 cells (eg, for derivatives and markers)
88273	chromosomal in situ hybridization, analyze 10-30 cells (eg, for microdeletions)
88274	interphase in situ hybridization, analyze 25-99 cells
88275	interphase in situ hybridization, analyze 100-300 cells
88280	Chromosome analysis; additional karyotypes, each study
88283	additional specialized banding technique (eg, NOR, C-banding)
88285	additional cells counted, each study

CODES	DESCRIPTION
88289	additional high resolution study
88291	Cytogenetics and molecular cytogenetics, interpretation and report
HCPCS Level II Codes	
S0265	Genetic counseling, under physician supervision, each 15 minutes
S3841	Genetic testing for retinoblastoma
S3842	Genetic testing for von hippel-lindau disease
S3844	DNA analysis of the connexin 26 gene (gjb2) for susceptibility to congenital, profound deafness
S3845	Genetic testing for alpha-thalassemia
S3846	Genetic testing for hemoglobin e beta-thalassemia
S3849	Genetic testing for Niemann-Pick disease
S3850	Genetic testing for sickle cell anemia
S3852	DNA analysis for apoe epsilon 4 allele for susceptibility to Alzheimer's disease
S3853	Genetic testing for myotonic muscular dystrophy
S3861	Genetic testing, sodium channel, voltage-gated, type v, alpha subunit (scn5a) and variants for suspected brugada syndrome
S3865	Comprehensive gene sequence analysis for hypertrophic cardiomyopathy
S3866	Genetic analysis for a specific gene mutation for hypertrophic cardiomyopathy (HCM) in an individual with a known HCM mutation in the family
S3870	Comparative genomic hybridization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or mental retardation

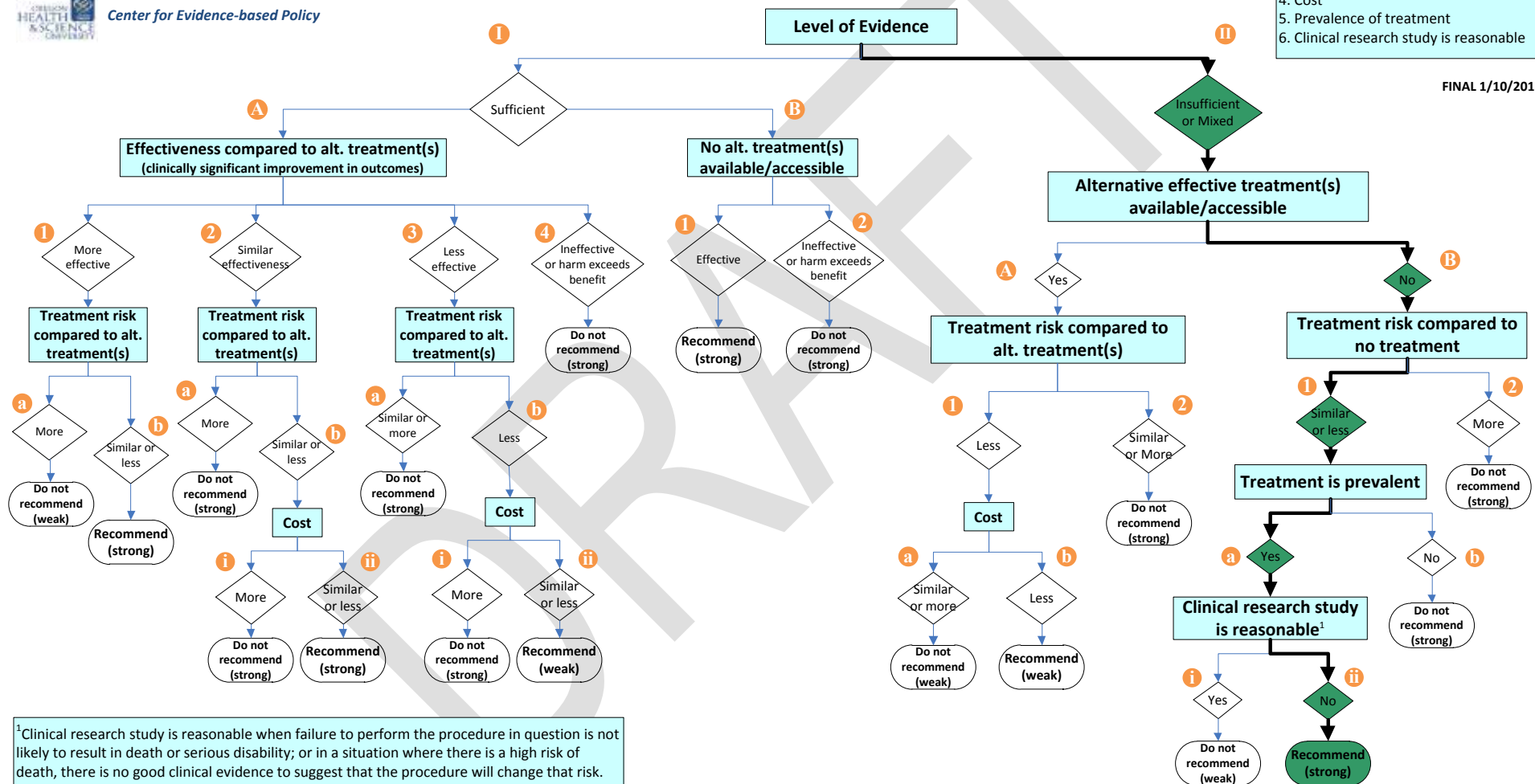
Note: Inclusion on this list does not guarantee coverage

Validated questionnaire to assess genetic risk in all pregnant women



Refer to *HERC Guidance Development Framework Principles* for additional considerations

- FINAL 1/10/2013**



Screening for thrombophilia



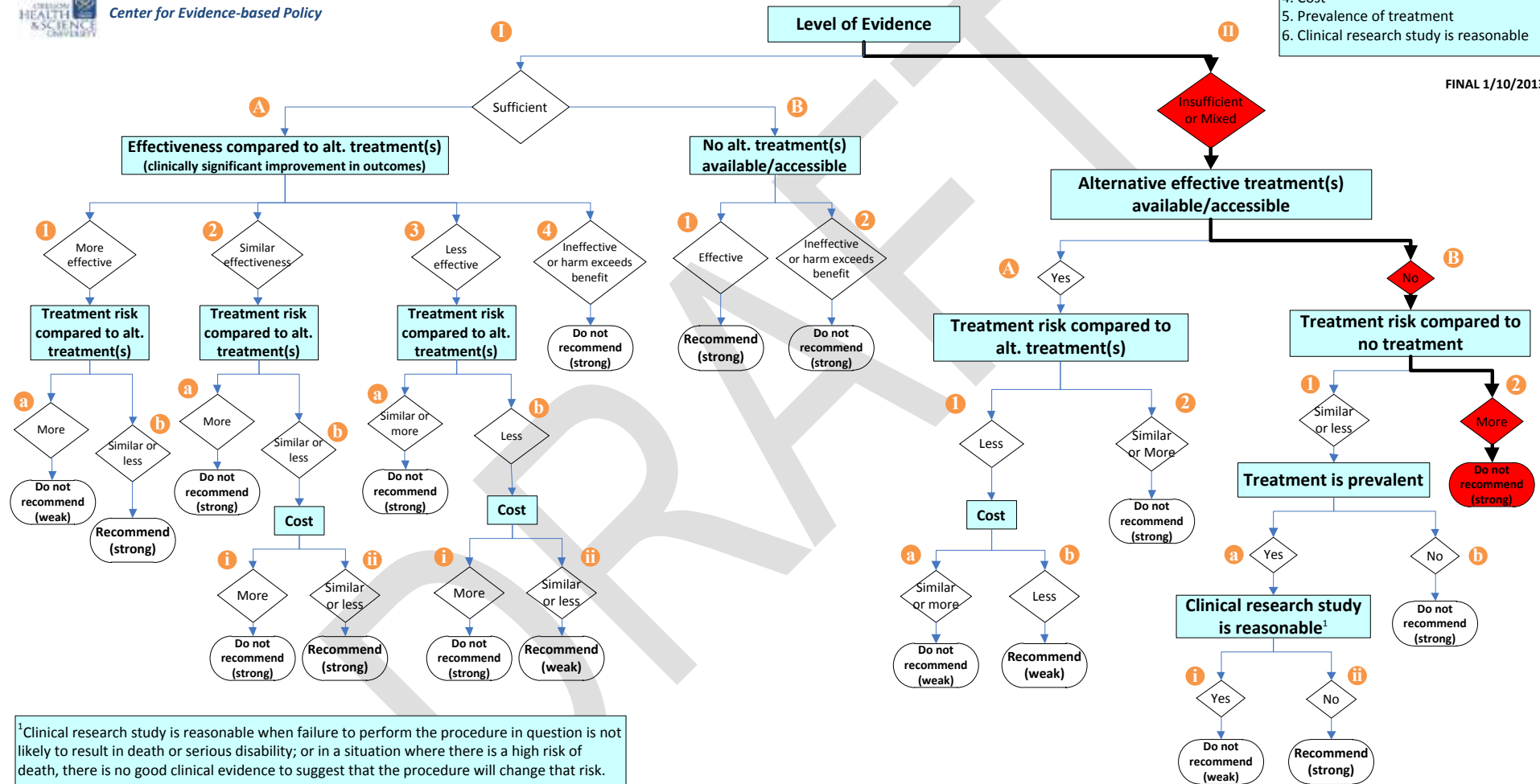
Center for Evidence-based Policy

HERC Guidance Development Framework

Refer to *HERC Guidance Development Framework Principles* for additional considerations

- Decision Point Priorities**
1. Level of evidence
 2. Effectiveness & alternative treatments
 3. Harms and risk
 4. Cost
 5. Prevalence of treatment
 6. Clinical research study is reasonable

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Array CGH testing when karyotype normal and structural anomaly on US; Screen high-risk ethnic groups for hemoglobinopathies; Aneuploidy screening in first or second trimester; CVS or amnio for + aneuploidy screen, maternal age > 34, fetal structural anomalies, + FH, elevated risk of neural tube defect or maternal request; Screening for Tay-Sachs carrier status using Hex A in high risk populations; Screening for CF carrier status; Screening for fragile X carrier status in women with +FH or risk factors; Screening of Ashkenazi Jewish population for specific genetic diseases; Expanded carrier screening



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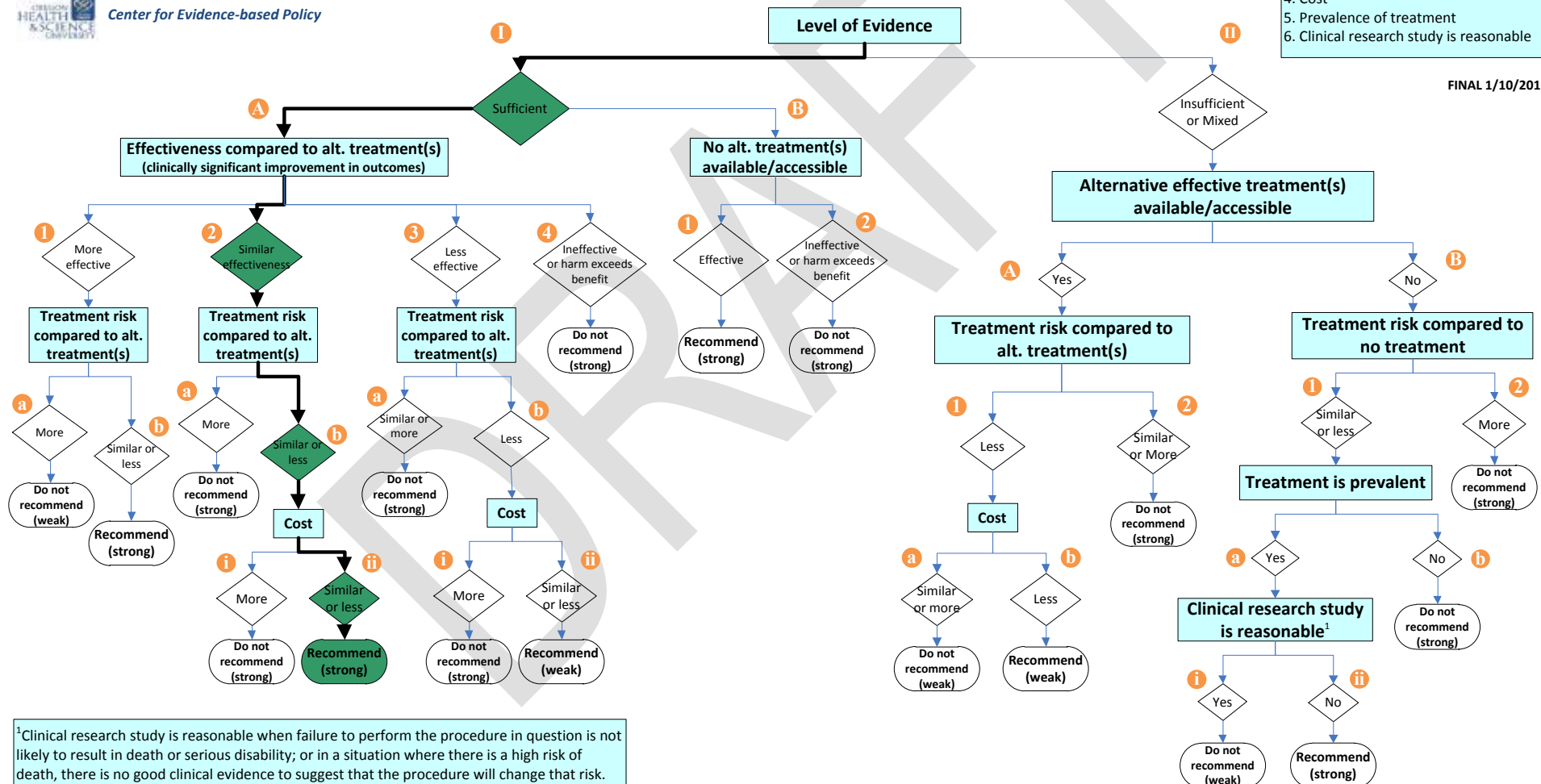
HERC Guidance Development Framework

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Decision Point Priorities

1. Level of evidence
2. Effectiveness & alternative treatments
3. Harms and risk
4. Cost
5. Prevalence of treatment
6. Clinical research study is reasonable

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Aneuploidy testing with QF-PCR; Aneuploidy testing with FISH



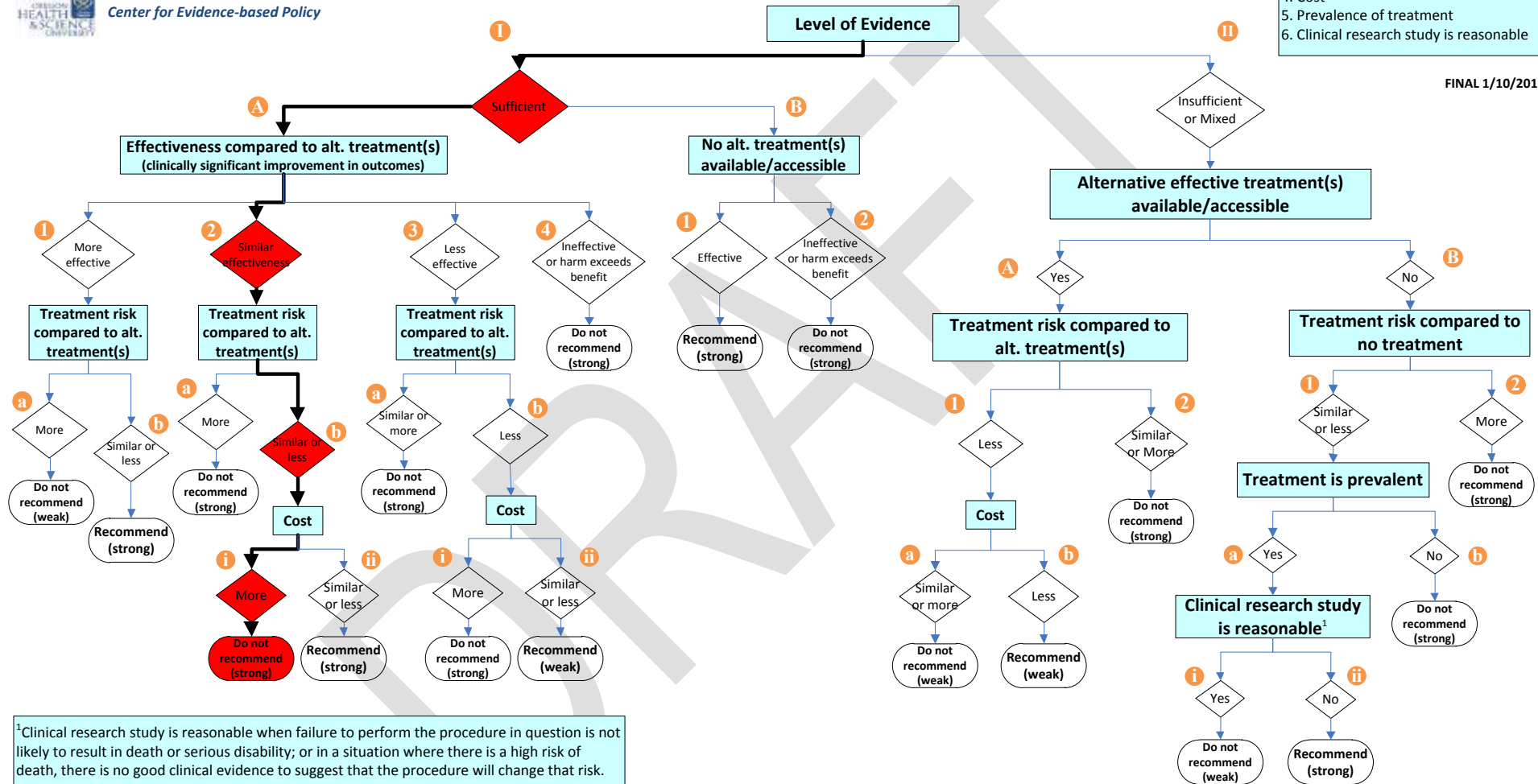
Center for Evidence-based Policy

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- Decision Point Priorities**
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 2. Effectiveness & alternative treatments
 3. Harms and risk
 4. Cost
 5. Prevalence of treatment
 6. Clinical research study is reasonable

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¹Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

Cell free fetal DNA testing



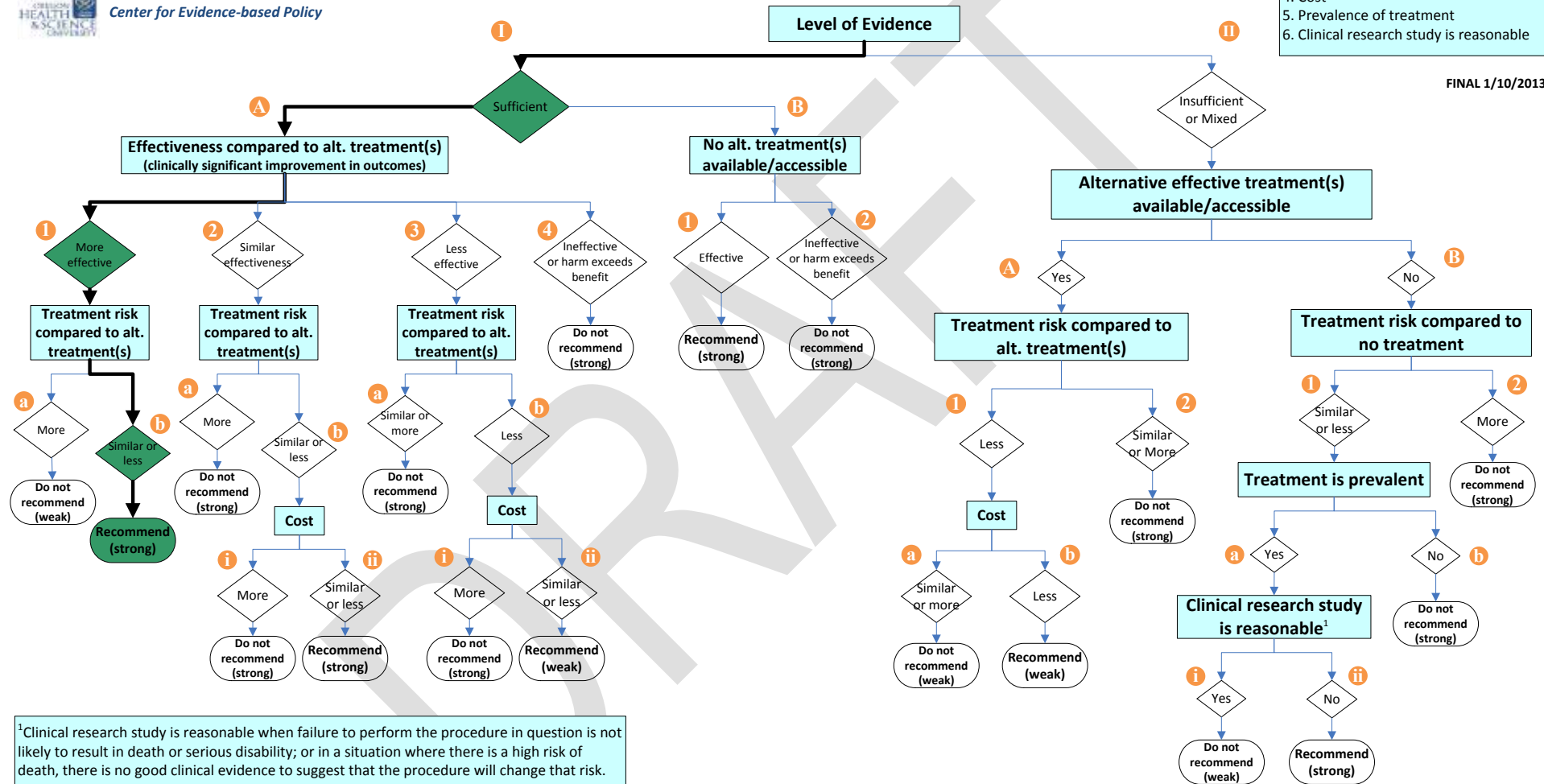
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- Decision Point Priorities**
1. Level of evidence
 2. Effectiveness & alternative treatments
 3. Harms and risk
 4. Cost
 5. Prevalence of treatment
 6. Clinical research study is reasonable

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Ultrasound for structural anomaly screen at 18-20 weeks; Fetal genetic analysis of fetuses at risk for fetal skeletal dysplasia based on US; Spinal muscular atrophy carrier screening



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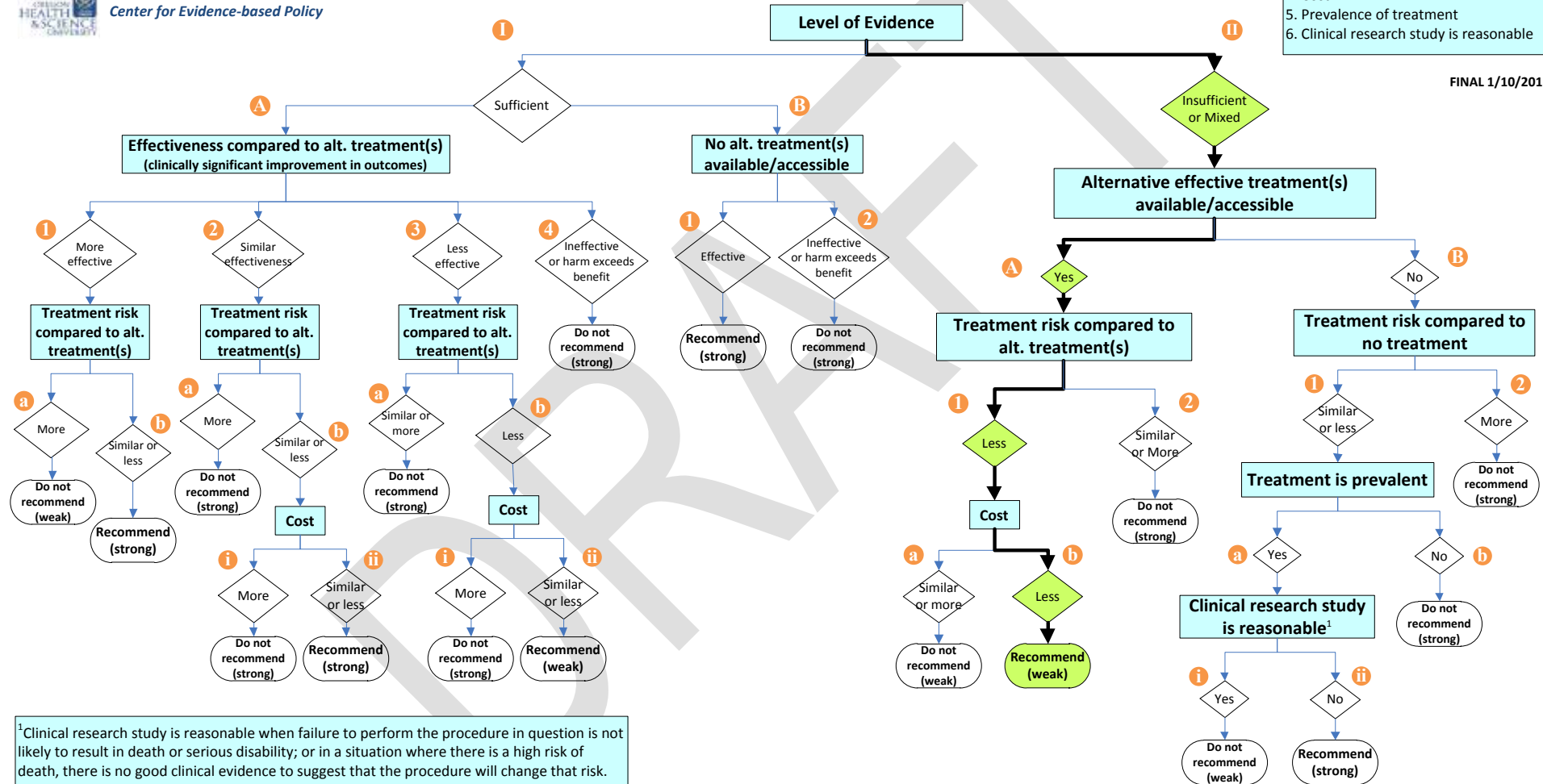
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Decision Point Priorities

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2. Effectiveness & alternative treatments
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6. Clinical research study is reasonable

FINAL 1/10/2013



HERC Coverage Guidance – Prenatal Genetic Testing Disposition of Public Comments

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Commenters

Identification	Stakeholder
A	<i>Oregon Medicaid Managed Care Medical Director</i>
B	<i>Verinata Health, Redwood City, CA</i>
C	<i>7 Physicians and 4 Genetic Counselors, Legacy Medical Group- Maternal Fetal Medicine, Portland, OR</i>
D	<i>6 Physicians and 4 Genetic Counselors, OHSU, Portland, OR</i>
E	<i>10 Portland-area Prenatal Genetic Counselors from the following organizations:</i> OHSU Dept. of OB/GYN, Division of Maternal Fetal Medicine Women's Health Associates, LLC, Northwest Perinatal Center Legacy Emanuel Hospital Maternal Fetal Medicine

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Public Comments Grouped by Topic

Stakeholder	#	Comment	Disposition
Invasive Aneuploidy Testing			
A	1	Comments regarding the prenatal genetic testing draft: A concern regarding universally offering genetic counseling and invasive aneuploidy testing for any woman over 34 years old, even if noninvasive screening is normal. Given funding priorities, and that this is a “weak” recommendation, is it appropriate for OHP benefits? Should this be reset to an older maternal age with a higher pretest probability of aneuploidy in the presence of negative screening? Unless you have good evidence to support counseling and invasive testing for mothers > 34 who have a negative noninvasive screen, it seems to me that should not be covered given the priorities of OHP funding.	EbGS agrees that the evidence pertaining to maternal age >34 does not warrant genetic counseling without additional indications of elevated risk. Guidance recommendation changed to reflect this.
A	2	Our Managed Care Plan is seeing tests beyond karyotyping requested (e.g. microarrays) as a routine for advanced maternal age, by the OHSU obstetrics/genetics group.	Guidance document only recommends coverage of array CGH if major fetal anomalies are apparent on imaging and karyotype is normal.
Cell Free Fetal DNA Testing			
B	3	We are writing in response to your Draft Coverage Guidance: Prenatal Genetic Testing, more specifically <i>Cell Free Fetal DNA Testing</i>. The proposed position of HERC is to NOT recommend coverage for the aforementioned type of prenatal testing due to ‘no evidence identified’ in support of its use. Please review the following and accompanying information as provided evidence in support of Cell Free Fetal DNA Testing and its use: Technology Assessments Sequencing-Based Tests to Determine Fetal Trisomy 21 from Maternal Plasma DNA, April 2013; Technology Evaluation Center (TEC): Blue Cross Blue Shield Association’s Office of Clinical Affairs in conjunction with Kaiser Permanente Medical Care Program. Evaluation criteria include, 1) The technology must have final approval from the appropriate governmental regulatory bodies; 2) The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes; 3) The technology must improve the net health outcome; 4) The technology must be as beneficial as any established alternatives; and, 5) The improvement must be attainable outside the investigational settings. Conclusion: ‘Based on the above, nucleic acid sequencing-based testing of	This citation is from one of the HERC trusted sources and indeed concluded that cell-free DNA testing for trisomy 21 meets TEC criteria for coverage in both high-risk and average risk women, based on 9 studies. Only one of these addressed average risk women. EbGS agrees that the evidence is sufficient to recommend coverage of cell-free fetal DNA testing in high-risk women, but not in average risk women. Guidance recommendation changed to reflect this.

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		maternal plasma for trisomy 21 with confirmatory testing of positive results (as is expected to be performed in a real-world clinical setting) in both high-risk women and average-risk women being screened for trisomy 21 meets the TEC criteria.'	
B	4	Fetal Aneuploidy Detection by Maternal Plasma DNA Sequencing, Part 2, October 2013; California Technology Assessment Forum (CTAF). Evaluation criteria: same as TEC (above). Recommendation #1: 'It is recommended that the use of cell free fetal DNA as a prenatal advanced screening test for fetal aneuploidy for Trisomy 21 and Trisomy 18 in high risk women meets CTAF criteria 1-5 for safety and efficacy and improvement in health outcomes.' Conclusion: 'In conclusion, cffDNA is a promising new technology with high sensitivity and specificity for the prediction of fetal aneuploidy, in particular T 21 and T18, when evaluated as an advanced screening test in high risk women. In high risk women, when used as an advanced screening test, it has the potential to reduce the number of invasive diagnostic procedures, with their associated risks of fetal loss.'	This TA (dated June 2012) also concludes that cell-free DNA testing for trisomy 21, 18 and 13 meets TEC criteria for coverage in high-risk women, based on 7 studies. See comment #3.
B	5	Professional Society Recommendations/Position Statements: The following societies have reviewed cell free fetal DNA testing technology and have adopted cautionary yet favorable positions on its use in the clinical setting. American College of Obstetricians and Gynecologists/Society for Maternal-Fetal Medicine (ACOG/SMFM): Committee Opinion 545: Noninvasive Prenatal Testing for Fetal Aneuploidy, Dec. 2012	ACOG recommendations state the following: <i>Patients at increased risk of aneuploidy can be offered testing with cell free fetal DNA. This technology can be expected to identify approximately 98% of cases of Down syndrome with a false-positive rate of less than 0.5%.</i> AND <i>Cell free fetal DNA testing should not be offered to low-risk women or women with multiple gestations because it has not been sufficiently evaluated in these groups.</i>
B	6	International Society for Prenatal Diagnosis (ISPD): Position Statement from the Aneuploidy Screening Committee on Behalf of the Board of the International Society for Prenatal Diagnosis, April 2013.	This guideline states: <i>Although rapid progress is being made in the development and validation of this technology, demonstration that in actual clinical practice the testing is sufficiently accurate, has low failure rates and can be provided in a timely fashion has not yet been provided.</i> They list 9 caveats highlighting the test limitations: <i>1. Reliable non-invasive maternal cf DNA aneuploidy screening methods have only been reported for trisomy 21 and 18. cfDNA</i>

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			screening results have been reported for trisomy 13 but the numbers are not large and efficacy appears to be less than for trisomies 21 and 18. cfDNA screening results have also been reported for sex chromosome aneuploidy and the efficacy is unacceptably low 2. There are insufficient data available to judge whether any specific cfDNA screening method is most effective 3. The tests should not be considered to be fully diagnostic and therefore are not a replacement for amniocentesis and CVS. Some affected pregnancies may not be detected and there may be false-positive results. 4. Analytic validity trials have been mostly focused on patients who are at high risk on the basis of maternal age or other screening tests. Efficacy in low risk populations has not yet been fully demonstrated. There are currently only limited data to suggest the test failure rate will not be appreciably higher for low-risk women and the false-positive rate also appears to be comparable. 5. There is insufficient information to know how well the test will perform in multiple gestation pregnancies that are discordant for trisomy but, theoretically, the detection of affected pregnancies could be lower than in singletons. When there has been a known early demise of a co-twin (“vanishing twin”), results may be inaccurate. 6. In cases where mosaicism is present (including confined placental mosaicism) results may be inaccurate. 7. In a proportion of cases there is insufficient fetal cfDNA in the maternal plasma specimen or there is test failure for other reasons (Table 2). It is not known what proportion of women with insufficient fetal cfDNA or a failed or uninterpretable test would have an informative repeat test result. In addition, one of the cfDNA screening methods classifies a proportion of results as “unclassified” when they are in fact at somewhat increased risk of aneuploidy. 8. Specific independently developed laboratory minimum standards, quality control, proficiency testing and inspection requirements have not yet been developed for this testing. It is expected that quality control standards will be developed and the ISPD strongly cautions

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			providers to seek out laboratory services that meet national guidelines for quality control and proficiency testing that is the current standard for other molecular tests. 9. It has not been demonstrated that the test can be provided in a cost-effective, timely, and equitable manner to total populations.
B	7	National Society of Genetic Counselors: Noninvasive Prenatal Testing/Noninvasive Prenatal Diagnosis: the position of the <i>National Society of Genetic Counselors</i>	This position statement of the NSGC, dated April 2012, states: <i>NSGC does not currently support NIPT as a routine, first-tier aneuploidy screening test in low-risk populations: To date, these technologies have been validated only in pregnancies considered to be at an increased risk for fetal aneuploidy, based on maternal age, family history, or positive serum and/or sonographic screening tests.</i> <i>Clinical studies show that MPS (massively parallel sequencing) effectively detects fetal trisomy 21, trisomy 13, and trisomy 18. MPS has not yet been proven efficacious in detecting other chromosomal abnormalities or single-gene disorders, and clinical trials for other technologies have not yet been published. NSGC recommends that pretest counseling for NIPT include information about the disorders that it may detect, its limitations in detecting these conditions, and its unproven role in detecting other conditions.</i>
B	8	Oregon's Commercial Insurance Reviews and Coverage In addition to the aforementioned favorable assessments and clinical professional societal recommendations, the national and regional payers have completed reviews of the Cell Free Fetal DNA Testing technology and found their use to be medically necessary and a covered benefit under their health plan offerings. Those payers with positive medical policy and coverage for Cell Free Fetal DNA testing and operating within Oregon include: • Aetna • Coventry • Humana • Health Net • UnitedHealthcare • Regence BCBS of Oregon	Thank you for providing this information. The EbGS makes its decisions based on evidence of effectiveness and harms, not on the basis of other payers' coverage policies.

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		- Providence Health Plan - ODS Health Plans - Lifewise of Oregon	
B	9	Costs While this test could be looked at as additive to the current prenatal screening care continuum and as such the program would incur increased costs, there is data and information to suggest that the utilization of the Cell Free Fetal DNA Testing could be off-set by the decrease in utilization of invasive procedures such as CVS and amniocentesis. Additionally, should there be unfavorable outcomes associated with the continued utilization of invasive procedures, costs associated with those outcomes can compound cost significantly; these unfavorable outcomes and associated costs could be mitigated with the inclusion of Cell Free Fetal DNA Testing in the prenatal care continuum. A study addressing both the utilization and cost impact of Cell Free Fetal DNA Testing is also attached. This study was conducted by Bridgehead International and is titled, <i>Clinical and Cost Consequences of Incorporating a Novel Non-Invasive Prenatal Test into the Diagnostic Pathway for Fetal Trisomies</i>; Journal of Managed Care Medicine, Nov. 2012.	This cost model assumes a cost for the cell-free DNA test (verifi™) of \$1200. Costs for other cffDNA tests range from \$795 to \$1900. Authors modeled a population of 5 million with 100,000 pregnancies annually. Model found a 66% reduction in invasive diagnostic induced miscarriages and that 38% more women received a T21 diagnosis. The model predicts that total costs for prenatal screening and diagnosis for fetal aneuploidies are reduced by 1% annually.
B	10	As a purveyor of one of the Cell Free Fetal DNA Testing options available to providers for prescribing to patients, we feel that in order to provide access and continuity of care across all populations residing in Oregon, HERC should adopt a favorable position on Cell Free Fetal DNA Testing and allow for its use. Thank you in advance for your review of the accompanying information of evidence support of Cell Free Fetal DNA Testing.	Thank you for your comments.
E	11	We are writing this letter in support of coverage for Non Invasive prenatal testing (NIPT) through cell free fetal DNA. While we applaud the Health Evidence Review Commission's decision to recommend coverage of aneuploidy screening, we disagree with the decision not to cover NIPT. The American College of Obstetrics & Gynecology and the Society for Maternal Fetal Medicine have both recommended noninvasive prenatal testing (NIPT) as a screening test for high-risk women. The National Society of Genetic Counselors and the International Society of Prenatal Diagnosis have also stated their approval of NIPT as an option for patients whose pregnancies are considered to be at an increased risk for certain	See comments #5, 6, and 7. Society for Maternal Fetal Medicine recommendations not cited or provided.

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		chromosome abnormalities.	
E	12	Without NIPT women whose pregnancies are at high risk (advanced maternal age, abnormal serum screening, abnormal ultrasound findings, previous pregnancy with aneuploidy) must choose between screening tests with lower detection rates and higher false positive rates versus an invasive procedure that may cause miscarriage. Furthermore, NIPT can be performed at any time in pregnancy after ~10 weeks gestation, providing valuable risk assessment information for women who may be outside of the recommended gestational age for any form of screening or invasive procedure.	Use of cffDNA testing does not necessarily obviate the need for invasive testing, since a positive result requires confirmation by CVS or amniocentesis. Also, cffDNA is only used to screen for trisomy 21 and 18. Women at high risk may still require additional testing. See comment #3.
E	13	Although not considered diagnostic, NIPT has been shown as a cost-effective tool in several U.S. studies. Studies by Song et al. (2013) and Ohno & Caughey (2013) have both shown that NIPT leads to improved detection of chromosome abnormalities with fewer false positives, fewer unnecessary invasive procedures, and lower rates of miscarriage in chromosomally-normal pregnancies. These studies have shown that in high-risk pregnancies (advanced maternal age, abnormal serum screening, abnormal ultrasound findings, previous pregnancy with aneuploidy), NIPT has lower total healthcare expenditures. For example, Song et al. estimated that NIPT would cost \$300,000,000 less than first trimester screening and \$500,000,000 less than traditional maternal serum screening.	Song 2013 is a CEA that modeled NIPT in women who were > 35 or those with a + conventional screening test, compared to first trimester screen and integrated screening method. Theoretical cohort was all US births in one year. Cost of test was \$795 in the model. Other tests cost more, with MaterniT21™ being the most expensive at \$1900. Ohno 2013 concludes that, in high risk women, NIPT used as a screening tool that requires invasive confirmation is more cost-effective than when it is used as a diagnostic tool (no confirmation, reproductive decision made based on NIPT only) and results in more false positive terminations than the number of procedure related losses in the those who undergo the invasive confirmation.
C	14	Cell Free Fetal DNA (cffDNA) testing We agree that cffDNA has not been evaluated as a primary screening test and should not be utilized in the general population or in multiple gestations at this time. However, there is quality evidence to support its use as an “advanced” or second line screening test. In such pregnancies (i.e. abnormal screening result), the use of cffDNA offers higher detection rates and lower false positive rates than historically utilized options. There is ample evidence to conclude cffDNA can detect 97-99% of pregnancies affected by either Down syndrome or Trisomy 18 in particular while maintaining a very low chance for a false positive result. Other conditions can also be detected, although this is currently based on lesser data.11-18	4 of the listed citations were included in the BCBS TEC assessment (see comment #3). One is the ACOG committee opinion (see comment #5) and one is the ISPD position statement (see comment #6). One is the ACMG statement on cffDNA: No direct recommendation is made, but the conclusions states: “The ACMG encourages providers of NIPS technology to make serious efforts to provide the more clinically relevant metrics—PPV and NPV. The ethical principle of distributive justice causes us to reflect on who will pay for NIPS and who should be insured for the procedure. No doubt NIPS costs will come down; however, for NIPS to establish roots in the perinatal aneuploidy screening paradigm, cost as a barrier to population-based screening must be minimized.”

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			The last citation is a fact sheet created by the National Coalition for Health Professional Education in Genetics and the National Society of Genetic Counselors.
C	15	CffDNA testing has been found to be a highly desired option for those women who do not wish diagnostic testing by CVS or amniocentesis. Declining to cover cffDNA testing forces families to either accept an option with a higher procedure related risk for loss or delaying testing until after delivery. We believe that cffDNA tests should be available to women who have a high pretest probability for positive findings (i.e. positive aneuploidy screen, enlarged NT measurement, or a structural anomaly on anatomic assessment of the fetus).19-22	Citation #19 is a SR of “factors influencing clinical use of NIPT”. Included 11 studies pertaining to attitudes and experiences with using the test, makes the following suggestion: “Consideration needs to be made with respect to the needs of specific patient groups before the introduction of NIPT into clinical practice. For example, although it may be appropriate to offer NIPT in high risk pregnancies, introduction for population screening may not be warranted without further research, public consultation and discussion at policy level to address concerns about the ethical and social implications.” Citation #20 is cohort study of women and health professionals that compared preferences between those groups for test attributes. They found women value avoidance of miscarriage most, while health professionals value accuracy most. Citation #21 is a narrative review and editorial that states “Although currently being integrated in some settings as a primary screening test for women at high risk of fetal aneuploidy, from a population perspective, a better option for noninvasive prenatal testing may be as a second-tier test for those patients who screen positive by conventional aneuploidy screening. How noninvasive prenatal testing will ultimately fit with the current prenatal testing algorithms remains to be determined. True cost–utility analyses will be needed to determine the actual clinical efficacy of this approach in the general prenatal population.” AND “The absence of guidelines for quality control and quality assurance for the laboratory testing is a significant concern. The methodologies are highly complex and the testing is subject to intense commercial competitive pressures.” AND

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			"In a recent publication on noninvasive prenatal testing in an average risk population of women undergoing first-trimester screening, noninvasive prenatal testing detected 55% of the total chromosomal abnormalities (eight of eight cases of trisomy 21 and two of three cases of trisomy 18), whereas first trimester screening detected 100% (all T21 and T18 as well as seven other deletions, duplications, and other abnormalities). Citation #22 is a best ethical practices statement funded by the NIH that makes 10 recommendations and concludes "Principal recommendations include the amendment of current informed consent procedures to include attention to the noninvasive nature of new testing and the potential for a broader range of results earlier in the pregnancy. We strongly recommend that tests should only be provided through licensed medical providers and not directly to consumers."
C	16	Some groups argue that cffDNA testing should also be used as a first line test for women of advanced maternal age. Until there is sufficient evidence to support the use of cffDNA as a primary screening test and proven to be cost effective, we do not support this policy. We recommend that all women interested in screening, regardless of age, be offered conventional screening and be offered cffDNA based testing (in addition to diagnostic testing) only in the event of a positive screen result. All positive cffDNA results should be confirmed by traditional diagnostic testing due to the risk for false positive results.	Thank you for your comment.
Noninvasive Aneuploidy Testing			
C	17	While we recognize that the task of narrowing choices for testing is arduous, we feel that optimal patient care requires us to ask for the inclusion of additional options. Timing is important as some couples when faced with information that can impact the long term health of an individual, may decide not to continue a pregnancy. Diagnostic testing (chorionic villus sampling (CVS) or amniocentesis) is available under the current recommendations. However, the recommended options for screening severely limit first trimester screening capabilities. Thus, the option for CVS is significantly curtailed.	Thank you for taking the time to comment.

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C	18	Aneuploidy screening: The commission has recommended four modalities. They have not commented on combined first trimester screening alone. The recommended methodologies might incorporate first trimester assessment of the nuchal translucency (NT) or in combination with serum analytes. However, the chosen methods either limit the capabilities of the first trimester screen (to limit false positive rates) or ignore it altogether. The bulk of the chosen methods delay full interpretation of risk until after 16 weeks, when first trimester diagnostic procedures opportunities have passed. This limits couple's choices and is incongruous with the commission's recommendation for CVS after a positive aneuploidy screen. We recommend combined first trimester screening (NT with HCG and PAPP-A) be added as a standalone screening option due to its high sensitivity, clinical availability, relatively low cost, and fast turnaround time in an early gestational window which would allow for counseling and further testing if desired.1-6	EbGS agrees that the first trimester screening option outlined in the NICE guideline should be one of the available screening options. Guidance recommendation changed to reflect this.
C	19	Screening with Ultrasound (US) The commission recommends anatomic assessment at 18-20 weeks, but does not comment on the use of first trimester US (particularly the assessment of the nuchal translucency). First trimester US provides important clinical information including: screening for structural anomalies, aneuploidy and/or genetic syndromes; providing early assessment of dating and viability (far more accurate than other clinical means); early recognition of multiple pregnancies including chorionicity, and detection of mullerian anomalies. Enlarged nuchal translucency (NT) measurements >95% for gestational age are known to increase the possibility for aneuploidy or structural anomaly, and NT measurements >99% also increase the risk for genetic syndromes as well. We recommend the option of NT measurements in all pregnancies in order to guide risk assessment for these issues. 7-10	NT is an element of stepwise sequential and contingency screening. Citations: #7 Ayas was a case series of 1063 pregnancies with increased NT. During the time period of this study, no biochemical 1st trimester screening tests were utilized. 78% of these fetuses had normal karyotype, but of those, 9% had structural defects or genetic disorders. #9 Mula is an abstract and editorial of a case series examining outcomes of 171 pregnancies with increased NT and normal karyotype. Of these, 28% did not survive due to miscarriage, termination or post natal death. Of the remaining infants, 10% had structural defects and 4% had severe neurodevelopmental impairment. For both of these studies, whether the anomalies would have been identified with a different aneuploidy screening methodology is not addressed. Citations #8 and #10 were published before the date of all 3 guidelines that informed this recommendation. The EbGS bases their

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			guidance documents on reviews of the literature that utilize the highest standards of evidence based medicine. Studies are included or excluded based on transparent, reproducible criteria; therefore the HTAS does not investigate individual studies. The HTAS assumes that the conclusions reached by the authors of these reviews weigh all the available evidence in accordance with the principles of evidence based medicine, and does not attempt to re-review the entire body of evidence to reach its own conclusions. EbGS does not see the need for a NT determination if an alternative screening method is chosen.
Carrier Screening			
C	20	Carrier screening: We would request that HERC consider the globalization of the population when making recommendations regarding carrier screening during pregnancy. Increasingly, parents report being of a mixed ethnic background and making screening determinations on this parameter alone is difficult. There is also emerging evidence that carrier frequencies in low risk populations may be higher than we would have thought. For instance, data from Counsyl indicate a high rate of carriers of traditional Ashkenazi Jewish conditions in individuals who do not report Jewish ancestry. 23 Due to these emerging trends, a carrier screening program will need to evolve to meet the needs of patients. Limiting screening based on ethnic background alone will increasingly miss at risk individuals. Guidelines based on general population data will likely be necessary to mirror the changes in ethnicity in the population.	Citation #23 is an analysis of the ethnicity of individuals who underwent routine carrier screening and had positive findings. The authors report that of the 23,453 individuals screened, 433 would not have been identified as disease carriers in accordance with conventional ethnicity-based screening paradigms. While EbGS acknowledges this trend, no specific changes to the guidance recommendations appear to be indicated.
Genetic Counseling			
D	21	Prenatal Genetic Counseling—Why it Matters All pregnant women can benefit from genetic counseling. While we appreciate the Health Evidence Review Commission’s coverage guidance for genetic counseling prior to CVS, amniocentesis, microarray testing, Fragile X screening and Spinal Muscular Atrophy screening, we implore them to recommend genetic counseling for all pregnant women. It is our opinion that the current recommendations will benefit only a select population of women having prenatal genetic screening and testing. We are concerned that genetic counseling services will not be available to	While evidence has not been presented supporting the utility of genetic counseling for all women, EbGS understands the importance of providing this service for the first and fourth bulleted examples. EbGS does not believe the 2nd and 3rd bullets are sufficient justification for this service.

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		women who may fall outside of these specific guidelines, including: • Women with a family history of a chromosome abnormality or genetic disorder • Women with an abnormal finding on ultrasound or other increased risk for aneuploidy who are request more information but do not intend to pursue CVS or amniocentesis • Women whose prenatal care provider is unable to unwilling to explain the risks, benefits and limitations of noninvasive prenatal screening options • Women who have been found to be a carrier for genetic conditions, such as CF, who desire further explanation and partner testing	
D	22	The American College of Obstetrics & Gynecology has recommended that all pregnant women be offered screening for genetic conditions including Down syndrome and cystic fibrosis (CF). Although obstetricians, midwives and family medicine physicians are expected to be the educated about genetic testing options in pregnancy, the complexity and number of screening options continue to evolve at a rapid pace.	EbGS does not disagree with these statements.
D	23	A 2009 ACOG survey found that almost half of Obstetricians felt their training was inadequate to counsel patients about first trimester screening options and only 31% of those surveyed had actually read the 2007 ACOG committee opinion regarding prenatal screening recommendations (Driscoll, et al. Screening for Down syndrome: Changing practice of Obstetricians. <i>American Journal of Obstetrics & Gynecology</i> , 2009; 200: 459).	Driscoll 2009 is a survey of ACOG members. With regard to the first statement, 40% of respondents felt that their training was less than adequate to counsel patients about 1 st trimester options. However, 98% stated that they were either somewhat or well qualified to counsel patients about Down's syndrome screening, presumably due to ongoing education.
D	24	Studies in the literature have stated that the information about genetic testing provided in the first prenatal visit is inadequate for ensuring informed autonomous decision-making (Bernhardt et al. Prenatal Genetic Testing: Content of Discussion between Obstetric Providers and Pregnant Women. <i>Obstetrics & Gynecology</i>, 1998: 91:648). The authors of such studies implore physicians to improve their practice with the help of genetic counselors. Prenatal genetic counselors are specifically trained to work with couples pre-conceptually and during the prenatal period to: • <i>Provide risk assessment</i> • <i>Interpret family history, personal health history and genetic tests results</i>	Bernhardt 1998 is a case series of 169 pregnant patients whose first prenatal visit was evaluated for presence and content of genetic counseling. EbGS does not believe this is sufficient evidence of the need for formal genetic counseling in all women.

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		• <i>Explain the risk, benefits and limitations of genetic screening and testing options</i> • <i>Provide education & supportive counseling</i> • <i>Ensure informed consent and patient autonomy</i>	
D	25	Providing prenatal genetic counseling services to all pregnant women will improve the quality of care. Genetic information and available genetic tests are expanding rapidly. Most physicians and nurses simply don't have the time to keep up with these changes.	Evidence of the need for genetic counseling in all women is lacking.
D	26	Providing prenatal genetic counseling services to call pregnant women will save money by avoiding inappropriate genetic tests, arranging for the tests that are both appropriate and economical, and by identifying people who do not need expensive screenings or treatments.	See comment #23.
C	27	Genetic Counseling: We agree with indications for genetic counseling approved by HERC, but feel that they may not be sufficient. One purpose of genetic counseling is to educate patients about testing options. Limiting genetic counseling as proposed jeopardizes patient care in limiting their access to quality information and jeopardizes coverage of the service if they opt for screening instead of diagnostic testing after genetic counseling. We would encourage a broader coverage of genetic counseling service to include pre-test counseling for aneuploidy screening (either in group or individual format). We believe that it is a useful service and is cost effective in helping to tailor testing based on parent's choices.²⁴⁻²⁵ In addition to the proposed guidelines, we request that post-test genetic counseling be covered in the event of a positive test result initiated through a genetic counseling process.	Citation #24 is a case series of 139 women that utilized a questionnaire to assess the decision-making process of pregnant women offered first trimester aneuploidy screening. Unclear how this study supports the need for genetic counseling for all women. Citation #25 is a review and discussion article. EbGS does not believe the evidence supports genetic counseling for all women.

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References Provided by Commenters

A	None submitted
B	References embedded in comments
C	References: 1 Pandya, PP, Kondylis A, Hilbert L, et al: Chromosomal defects and outcome in 1015 fetuses with increased nuchal translucency. <i>Ultrasound Obstet Gynecol</i> 1995;5:15-9. 2 Wapner R, Thom E, Simpson JL, et al. First-trimester screening for trisomies 21 and 18. <i>N Engl J Med</i> 2003;349:1405-1413. 3 Malone FD, Canick JA, Ball RH, et al. First-trimester or second-trimester screening, or both, for Down's syndrome. <i>N Engl J Med</i> 2005;353:2001-2011. 4 Wald NJ, Rodeck C, Hackshaw AK, et al. First and second trimester antenatal screening for Down's syndrome: The results of the Serum, Urine and Ultrasound Screening Study (SURUSS). <i>J Med Screen.</i> 2003;10:56-104. 5 Jenkins TM, Wapner RJ. Integrated screening for Down's syndrome. <i>N Engl J Med</i> 1999;341:1935. 6 Nicholaides KH, Spencer K, Avgidou K et al. Multicenter study of first-trimester screening for trisomy 21 in 75821 pregnancies: Results and estimation of the potential impact of individual risk orientated two-stage first trimester screening. <i>Ultrasound Obstet Gynecol</i> 2005; 25:221-226. 7 Ayras O, Tikkanen M, Eronen M, et al. Increased nuchal translucency and pregnancy outcome: a retrospective study of 1063 consecutive singleton pregnancies in a single referral institution. <i>Prenatal Diagnosis</i> 2013;33: 1. 8 Souka AP, von Kaisenberg CS, Hyett JA, et al. Increased nuchal translucency with normal karyotype. <i>Am J Obstet Gynecol</i> 2005;192:1005. 9 Mula R, Gonce A, Bannas M, et al. Increased Nuchal Translucency and Normal Karyotype: Perinatal and Pediatric Outcomes at 2 Years of Age. <i>Ultrasound Obstet Gynecol</i> 2012;39:34. 10 Werner EF, Pastore LM, Karns LB, et al. Patient preferences for screening in the first trimester. <i>Prenat Diagn</i> 2008;28:1521. 11 Walsh JM and Goldberg JD. Fetal aneuploidy by maternal plasma DNA sequencing: a technology assessment. <i>Prenat Diagn</i> 2013;33:514. 12 Ashoor G, Syngelaki A, Wagner M, et al. Chromosome-selective sequencing of maternal plasma cell-free DNA for first trimester detection of trisomy 21 and trisomy 18. <i>Am J Obstet Gynecol</i> 2012; 206:322.e1-5 13 Ehrich M, Deciu C, Zweifelhofer T, et al. Noninvasive detection of fetal trisomy 21 by sequencing of DNA in maternal blood: a study in a clinical setting. <i>Am J Obstet Gynecol</i> 2011;204:205.e1-11. 14 Non-Invasive Prenatal Testing (NIPT) Factsheet. NCHPEG+NSGC 2012. 15 Noninvasive prenatal testing for fetal aneuploidy. Committee Opinion No. 545. American College of Obstetricians and Gynecologists. <i>Obstet Gynecol</i> 2012;120:1532-4. 16 Position statement from the Aneuploidy Screening Committee on behalf of the board of the International Society for Prenatal Diagnosis. International Society for Prenatal Diagnosis. April 2013. 17 Gregg A, Gross S, Best R et al. ACMG statement on noninvasive prenatal screening for fetal aneuploidy. <i>Genet Med</i> 2013;15:395-8. 18 Sehnert AJ, Rhees B, Comstock D, et al. Optimal Detection of Fetal Chromosomal Abnormalities by Massively Parallel DNA Sequencing of Cell-Free Fetal DNA from Maternal Blood. <i>Clinical Chemistry</i> 2011;57:1042. 19 Skirton H and Patch C. Factors affecting the clinical use of non-invasive prenatal testing: a mixed methods systematic review. <i>Prenatal Diagnosis</i> 2013;33:532. 20 Hill M, Fisher J, Chitty LS, and Morris S. Women's and health professionals' preferences for prenatal tests for Down syndrome: a discrete choice experiment to contrast noninvasive prenatal diagnosis with current invasive tests. <i>Genet Med</i> 2012;14:905.

HERC Coverage Guidance – Prenatal Genetic Testing Disposition of Public Comments

	21 Norton ME, Rose NC, and Benn P. Noninvasive Prenatal Testing for Fetal Aneuploidy: Clinical Assessment and a Plea for Restraint. <i>Obstet Gynecol</i> 2013;121:847. 22 Allyse MA, Sayres LC, Havard, M, et al. Best ethical practices for clinicians and laboratories in the provision of noninvasive prenatal testing. <i>Prenatal Diagnosis</i> 2013, 33, 1–6. 23 Lazarin G, Haque I, Nazareth S et al. An empirical estimate of carrier frequencies for 400+ casual Mendelian variants: results from an ethnically diverse clinical sample of 23453 individuals. <i>Genet Med</i> 2013;15:178-186. 24 Farrell RM, Nutter B, and Agatista PK. Meeting patients’ education and decision-making needs for first trimester prenatal aneuploidy screening. <i>Prenat Diagn</i> 2011;31:1222. 25 Pergament E, and Pergament D. Reproductive decisions after fetal genetic counseling. <i>Best Practice & Research Clinical Obstetrics and Gynaecology</i> 2012;26:517.
D	References embedded in comments
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CG - Femoroacetabular Impingement Syndrome

Question: How should the Coverage Guidance – *Femoroacetabular impingement syndrome* be applied to the Prioritized List?

Question source: Health Technology Assessment Subcommittee

HTAS approved 9/23/13 Draft Coverage Guidance Box

:

HERC COVERAGE GUIDANCE

Surgery for femoroacetabular impingement (FAI) syndrome is recommended (*strong recommendation*) for coverage in patients who meet all of the following criteria:

- Adult patients who are younger than 55 years of age, or adolescent patients who are skeletally mature with documented closure of growth plates; and
- Other sources of pain have been ruled out (e.g., lumbar spine pathology, SI joint dysfunction, sports hernia); and
- Pain unresponsive to physical therapy and other non-surgical management and conservative treatments (e.g., restricted activity, cortisone injections, nonsteroidal anti-inflammatory drugs) of at least three months duration, or conservative therapy is contraindicated; and
- Moderate-to-severe persistent hip or groin pain that significantly limits activity and is worsened by flexion activities (e.g., squatting or prolonged sitting); and
- Positive impingement sign (i.e., sudden pain on 90 degree hip flexion with adduction and internal rotation or extension and external rotation); and
- Radiographic confirmation of FAI morphology (e.g., pistol-grip deformity, alpha angle greater than 50 degrees, coxa profunda, and/or acetabular retroversion); and
- Do not have advanced osteoarthritis (i.e., Tönnis* grade 2 or 3) or severe cartilage damage (i.e., Outerbridge* grade III or IV).

Prioritized List Status:

- 1) Diagnosis code: there is no specific ICD-9 diagnosis code for FAI. Coding standards recommend using 719.85 (Other specified disorders of joint, pelvic region and thigh) which is currently on line 550 DEFORMITIES OF UPPER BODY AND ALL LIMBS. Also used is 718.05 (Articular cartilage disorder, pelvic region and thigh) which is also on line 550
- 2) Treatment codes: there is no specific CPT code for treatment of FAI. Treatment is generally billed with one or more of the following CPT codes, all of which are currently Excluded:
 - a. 29914 Arthroscopy, hip, surgical; with femoroplasty (ie, treatment of cam lesion)
 - b. 29915 Arthroscopy, hip, surgical; with acetabuloplasty (ie, treatment of pincer lesion)
 - c. 29916 Arthroscopy, hip, surgical; with labral repair
- 3) Also used as a treatment code is CPT 29862 (Arthroscopy, hip, surgical; with debridement/shaving of articular cartilage (chondroplasty), abrasion arthroplasty, and/or resection of labrum) which is on lines 143,161,297,336,384,406,550.
- 4) Lines with major hip diagnoses:
 - a. Line 297 DEFORMITY/CLOSED DISLOCATION OF JOINT

CG - Femoroacetabular Impingement Syndrome

- b. Line 384 RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, OSTEOCHONDRITIS DISSECANS, AND ASEPTIC NECROSIS OF BONE

HERC Staff Recommendations:

- 1) Add ICD-9 719.85 (Other specified disorders of joint, pelvic region and thigh) and 718.05 (Articular cartilage disorder, pelvic region and thigh) to Line 384 RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, OSTEOCHONDRITIS DISSECANS, AND ASEPTIC NECROSIS OF BONE
 - a. For the ICD-10 Prioritized List, add M24.15x (Other articular cartilage disorders, hip) and M25.85x (Other specified joint disorders, hip) to line 384
- 2) Keep 719.85/M25.85x and 718.05/M24.15x on line 550 DEFORMITIES OF UPPER BODY AND ALL LIMBS
- 5) Add CPT 29914 [Arthroscopy, hip, surgical; with femoroplasty (ie, treatment of cam lesion)], 29915 [Arthroscopy, hip, surgical; with acetabuloplasty (ie, treatment of pincer lesion)], and 29916 (Arthroscopy, hip, surgical; with labral repair) to line 384
- 6) Advise DMAP to remove 29914-29916 from the Excluded List
- 7) Adopt the following guideline for line 384:

GUIDELINE NOTE XXX FEMOROACETABULAR IMPINGEMENT SYNDROME

Line 384

ICD-9 719.85 (Other specified disorders of joint, pelvic region and thigh)/ICD-10 M25.85x (Other specified joint disorders, hip), ICD-9 718.05 (Articular cartilage disorder, pelvic region and thigh)/ICD-10 M24.15x (Other articular cartilage disorders, hip) and CPT codes 29914-29916 (Arthroscopy, hip, surgical) are included on line 384 only for the diagnosis and treatment of femoroacetabular impingement syndrome.

Surgery for femoroacetabular impingement syndrome is included on this line only for patients who meet all of the following criteria:

- 1) Adult patients who are younger than 55 years of age, or adolescent patients who are skeletally mature with documented closure of growth plates; and
- 2) Other sources of pain have been ruled out (e.g., lumbar spine pathology, SI joint dysfunction, sports hernia); and
- 3) Pain unresponsive to physical therapy and other non-surgical management and conservative treatments (e.g., restricted activity, cortisone injections, nonsteroidal anti-inflammatory drugs) of at least three months duration, or conservative therapy is contraindicated; and
- 4) Moderate-to-severe persistent hip or groin pain that significantly limits activity and is worsened by flexion activities (e.g., squatting or prolonged sitting); and
- 5) Positive impingement sign (i.e., sudden pain on 90 degree hip flexion with adduction and internal rotation or extension and external rotation); and
- 6) Radiographic confirmation of FAI (e.g., pistol-grip deformity, alpha angle greater than 50 degrees, coxa profunda, and/or acetabular retroversion); and
- 7) Do not have advanced osteoarthritis (i.e., Tönnis* grade 2 or 3) and/or severe cartilage damage (i.e., Outerbridge* grade III or IV).

HEALTH EVIDENCE REVIEW COMMISSION (HERC)
COVERAGE GUIDANCE: HIP SURGERY PROCEDURES FOR
FEMOROACETABULAR IMPINGEMENT SYNDROME

DRAFT for VbBS Meeting Materials 10/10/2013

HERC COVERAGE GUIDANCE

Surgery for femoroacetabular impingement (FAI) syndrome is recommended (*strong recommendation*) for coverage in patients who meet all of the following criteria:

- Adult patients who are younger than 55 years of age, or adolescent patients who are skeletally mature with documented closure of growth plates; and
- Other sources of pain have been ruled out (e.g., lumbar spine pathology, SI joint dysfunction, sports hernia); and
- Pain unresponsive to physical therapy and other non-surgical management and conservative treatments (e.g., restricted activity, cortisone injections, nonsteroidal anti-inflammatory drugs) of at least three months duration, or conservative therapy is contraindicated; and
- Moderate-to-severe persistent hip or groin pain that significantly limits activity and is worsened by flexion activities (e.g., squatting or prolonged sitting); and
- Positive impingement sign (i.e., sudden pain on 90 degree hip flexion with adduction and internal rotation or extension and external rotation); and
- Radiographic confirmation of FAI morphology (e.g., pistol-grip deformity, alpha angle greater than 50 degrees, coxa profunda, and/or acetabular retroversion); and
- Do not have advanced osteoarthritis (i.e., Tönnis* grade 2 or 3) or severe cartilage damage (i.e., Outerbridge* grade III or IV).

*See Appendix D for description of Tönnis and Outerbridge grading systems.

Note: Definitions for strength of recommendation are provided in Appendix A GRADE Element Description

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed

FAI CG-Draft-10-02-13b

by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Health Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

EVIDENCE SOURCES

Washington State Health Care Authority Health Technology Assessment Program. (2011). *Hip surgery procedures for treatment of femoroacetabular impingement syndrome: Health technology assessment*. Retrieved from <http://www.hta.hca.wa.gov/fai.html>

National Institute for Health and Clinical Excellence. (2011a). *Interventional Procedure Guidance 403: Open femoro-acetabular surgery for hip impingement syndrome*. London: National Institute for Health and Clinical Excellence. Retrieved from <http://guidance.nice.org.uk/IPG403>

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National Institute for Health and Clinical Excellence. (2011d). *Interventional procedure overview of arthroscopic femoro-acetabular surgery for hip impingement syndrome*. London: National Institute for Health and Clinical Excellence. Retrieved from <http://guidance.nice.org.uk/IPG408>

The summary of evidence in this document is derived directly from this evidence sources, and portions are extracted verbatim.

SUMMARY OF EVIDENCE

Clinical Background

Femoroacetabular impingement (FAI) syndrome is a recently recognized diagnosis in primarily younger individuals where relatively minor abnormalities in the joint (orientation or morphology) are thought to cause friction/impingement and pain. It is theorized that FAI starts the breakdown of cartilage, leading to osteoarthritis. There are two types of FAI: cam impingement (non-spherical femoral head or abnormality at the head-neck

junction) and pincer impingement (deep or retroverted acetabulum resulting in overcoverage of the femoral head). Proponents believe that surgical correction of the impinging deformities will alleviate the symptoms and retard the progression of osteoarthritis degeneration. Surgery to correct FAI includes arthroscopy, open dislocation of the hip and arthroscopy combined with a mini-open approach. The purpose of the surgery is to remove abnormal outgrowths of bone and damaged cartilage, and to reshape the femoral neck to ensure that there is sufficient clearance between the rim of the acetabulum and the neck of the femur. The causes of hip pain, the natural history of FAI and its relationship to osteoarthritis are unclear, and the case definition and selection criterion of patients for this procedure is uncertain. Furthermore, questions remain about the efficacy and effectiveness, safety and cost effectiveness of hip surgery for FAI.

Evidence Review

The evidence review addressed questions concerning case definition, evaluation of treatment outcomes, effectiveness and safety of hip surgery for FAI. To address the question of case definition, the most consistent case definition of FAI (cam or mixed) includes hip/groin pain, positive clinical impingement test, and an α -angle >50 - 55° . There is no evidence that the diagnosis of FAI can be obtained from clinical exam. One clinical test, the impingement sign, had a positive and negative predictive value of 86% and 79% in one study where the prevalence of FAI was 50%; however, in another study, the interobserver reliability of the impingement sign was only moderate. Even though the α -angle showed moderate to high interobserver reliability in several studies, it had poor diagnostic value in identifying FAI. Other imaging tests assessing abnormalities of the femur and acetabulum had variable degrees of reliability, but no others were tested for diagnostic validity.

Regarding outcome measures to evaluate the effectiveness of hip surgery for FAI, seven hip outcome measures were commonly used in the FAI patient population, but only three have undergone psychometric analysis in FAI (Hip Outcome Score, German version [HOS-D] and the modified Western Ontario and McMaster Universities Arthritis Index [M-WOMAC] or young hip-pain patients Nonarthritic Hip Score [NAHS]). Reliability was inadequately tested for all three instruments. The minimal clinically important difference was defined in only one measure, the HOS-D, and found to be 9 points for the activities of daily living subscale and 6 points for the sports subscale in FAI patients.

Regarding the efficacy of hip surgery for FAI, there are no randomized controlled trials (RCTs) available to assess the short- or long-term efficacy of FAI surgery compared with no surgery. Comparative evidence for this condition is limited to one retrospective

cohort study comparing FAI surgery to conservative treatment, and four retrospective studies comparing various surgical treatments.

The only study to compare FAI surgery to no surgery included 17 patients (22 hips) who underwent three different treatments: nonoperative care with physiotherapy and anti-inflammatory medications, arthroscopy or open dislocation, and total hip replacement (THA). There were nine patients (10 hips) in the nonoperative group, six patients (eight hips) in the FAI surgery group, and two patients (four hips) in the THA group. The authors gave no indication of how these patients were selected or how many patients overall may have been eligible for the study; they simply stated that radiographic findings of osseous bump deformities on the anterolateral head-neck junction were found in all patients along with typical symptoms of FAI. They did, however, admit that the treatment received was based according to clinical and radiographic findings and MRI, thus acknowledging the potential of confounding by indication. Those with moderate clinical symptoms but morphological signs of degenerative destruction of the hip joints underwent nonoperative treatment. Those with labral defects but only minor cartilage destruction on MRI underwent FAI surgery. The two patients who received THA did so as a result of having severe signs of osteoarthritis on radiographs. The authors provide no information regarding the patient selection process or loss to follow-up. There was no description of baseline characteristics apart from the mean age of patients. With respect to age, there were potentially important differences in ages of the patients among the three treatment groups. Only pain and return to work/sports are reported at final follow-up, with patients in the conservative group showing the poorest results overall: none were pain free at final follow-up compared with 100% of the patients in both surgical groups. Only 67% had returned to their previous work or sports level again compared with 100% of the patients in both surgical groups. It is difficult to draw any conclusions from this study as the patient groups compared were clearly different in many characteristics.

Of the other four cohort studies, two compared labral debridement with labral fixation, and two compared arthroscopic debridement and osteoplasty with arthroscopic debridement alone. Overall, none of these studies demonstrate that one specific treatment results in better outcomes than another (surgery versus no surgery, labral debridement versus refixation, osteoplasty versus no osteoplasty). Several case series report improvement in pain, patient reported and clinician reported hip outcome scores, patient satisfaction and return to normal activities following FAI surgery. However, whether this improvement is a result of the surgery, or the postoperative rehabilitation, or the change in activity subsequent to the surgery or placebo is not known. Approximately 8% of patients diagnosed with FAI who undergo surgery in published series go on to have a total hip arthroplasty within 3 years. There are no data available to assess long-term effectiveness of FAI surgery compared with no surgery. There are

no data yet published to test the hypothesis that FAI surgery prevents or delays hip osteoarthritis or the need for total hip arthroplasty.

Regarding the safety of hip surgery for FAI, the risk of reoperation (other than conversion to THA) occurred in 4% (arthroscopy and open dislocation) and 9% of the patients (mini-open). There was only one reported head-neck fracture (0.1%) and no reports of AVN, osteonecrosis or trochanteric nonunion. Heterotopic ossification occurred in 2% to 3% of those receiving arthroscopy or mini-open, and 6% in those receiving open dislocation. Neurological complications (nerve palsy, paresthesia, and neuropraxia) were rare in those receiving arthroscopy or open dislocation; however, they occurred in 22% of 258 hips undergoing a mini-open procedure. Most were transient in nature.

[\[Evidence Source\]](#)

The National Institute for Clinical Excellence issued interventional procedure guidances on arthroscopic and open surgery for FAI in September and July 2011, respectively. Both guidances state that current evidence on the efficacy of arthroscopic or open femoro–acetabular surgery for hip impingement syndrome is adequate in terms of symptom relief in the short and medium term. With regard to safety, there are well recognized complications. Therefore this procedure may be used provided that normal arrangements are in place for clinical governance, consent and audit with local review of outcomes. They have established a registry to track long term outcomes of these procedures.

The literature review conducted to inform the NICE guidance consisted of one non-randomized controlled study and seven case series for the open procedure, and three non-randomized controlled studies, five case series and one case report for the arthroscopic procedure. The reviews report the following regarding the evidence base:

- Little or no controlled data are available comparing the procedure with other interventions or against natural history.
- A range of outcome assessment scales are used; validation of these scales is often not reported.
- The description of hip impingement pathology/lesions is not well defined in all studies.
- The intervention required is usually individualized to each patient, making comparison between studies difficult.

Study quality is generally poor, with little prospective data collection in case series.

[\[NICE IPG 403, NICE IPG408\]](#)

Evidence Summary

The most consistent case definition of FAI (cam or mixed) includes hip/groin pain, positive clinical impingement test, and an α -angle >50 - 55° ; the predictive value of the impingement test ranges from 79 to 86%, while the α -angle has poor diagnostic value. Seven hip outcome measures are commonly used in the FAI patient population, but only three have undergone psychometric analysis in FAI, and reliability has been inadequately tested for all three. There are no data available to assess the short- or long-term efficacy of FAI surgery compared with no surgery, and no evidence that one specific treatment results in better outcomes than another. Regarding safety, the risk of reoperation (other than conversion to THA) is 4% to 9%, and heterotopic ossification occurs in 2% to 6% of patients, while neurological complications occur in up to 22% of patients.

After reviewing the available evidence including the lack of RCTs comparing FAI surgery to conservative care, as well as non-RCT comparative data demonstrating non-superiority of surgery, the WA HTA Clinical Committee concluded that the evidence was insufficient to recommend coverage of the procedure. The National Institute for Clinical Excellence has issued a guidance allowing for use of both arthroscopic and open procedures, despite a poor quality evidence base. They have established a registry to track long term outcomes.

GRADE-INFORMED FRAMEWORK

The HERC develops recommendations by using the concepts of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for carrying out the steps involved in developing recommendations. There are four elements that determine the strength of a recommendation, as listed in the table below. The HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Balance between desirable and undesirable effects, and quality of evidence, are derived from the evidence presented in this document, while estimated relative costs, values and preferences are assessments of the HERC members.

Indication	Balance between desirable and undesirable effects	Quality of evidence*	Resource Allocation	Values and preferences	Coverage Recommendation
Surgery for FAI after failure of conservative management, including physical therapy	Unclear Case control series suggest benefit but have high risk of bias. There is some risk of adverse effects from surgery.	Very low	Unknown at this time. Surgical intervention is generally more costly than conservative care in the short term. However a successful surgery may prevent disability-related costs.	Low variability. Younger patients would generally want to avoid total hip replacement if there are effective alternatives. Patient preferences make a future controlled trial for this service unlikely.	Surgery for femoroacetabular impingement syndrome is recommended for coverage (<i>strong recommendation</i>)

*The Quality of Evidence rating was assigned by the primary evidence source, not the HERC Subcommittee

Note: GRADE framework elements are described in Appendix A

POLICY LANDSCAPE

No quality measures were identified when searching the [National Quality Measures Clearinghouse](#).

COMMITTEE DELIBERATIONS – HTAS

In its review of public comment, the HTAS elected to make a strong recommendation for coverage for FAI surgery for selected patients despite insufficient evidence of effectiveness. This decision resulted from a discussion of the guidance development framework in which the subcommittee found no alternative effective treatments for patients who have met the criteria described in the recommended draft coverage guidance language. Based on this pathway the subcommittee found that there was similar or less risk with than no treatment. The subcommittee also found that treatment is prevalent and that further research is not reasonable at this time as it would be difficult to recruit patients. Based on expert input and information from other payers, the subcommittee adopted coverage criteria to restrict the procedure to patients who have failed conservative therapy.

COMMITTEE DELIBERATIONS – VBBS

Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

Appendix A. GRADE Element Descriptions

Element	Description
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Resource allocation	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted

Strong recommendation

In Favor: The subcommittee is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Against: The subcommittee is confident that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Weak recommendation

In Favor: the subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Against: the subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Quality of evidence across studies for the treatment/outcome

High = Further research is very unlikely to change our confidence in the estimate of effect.

Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low = Any estimate of effect is very uncertain.

Appendix B. Applicable Codes

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
715-715.9	Osteoarthritis
718.05	Articular cartilage disorder, pelvic region
718.45	Contracture of joint, pelvic region and thigh
718.65	Unspecified intrapelvic protrusion acetabulum, pelvic region and thigh
718.85	Other joint derangement, not elsewhere classified
718.95	Unspecified derangement of joint
719.45	Pain in joint, pelvic region and thigh
719.55	Stiffness of joint, not elsewhere classified, pelvic region and thigh
719.7	Difficulty in walking
719.85	Other specified disorders of join, pelvic region and thigh
719.95	Unspecified disorder of joint, pelvic region and thigh
736.30	Acquired deformities of hip, unspecified deformity
736.39	Acquired deformities of hip, other
ICD-9 Volume 3 (Procedure Codes)	
80.15	Other Arthrotomy, Hip
80.25	Arthroscopy, Hip
80.45	Division Of Joint Capsule, Ligament, Or Cartilage; Hip
81.40	Repair Of Hip, Not Elsewhere Classified
CPT Codes	
29914	Arthroscopy, hip, surgical; with femoroplasty (i.e., treatment of cam lesion)
29915	Arthroscopy, hip, surgical; with acetabuloplasty (i.e., treatment of pincer lesion)
29916	Arthroscopy, hip, surgical; with labral repair
HCPCS Level II Codes	
None	

Note: Inclusion on this list does not guarantee coverage

Appendix C. HERC Guidance Development Framework

Surgery for FAI Syndrome



Center for Evidence-based Policy

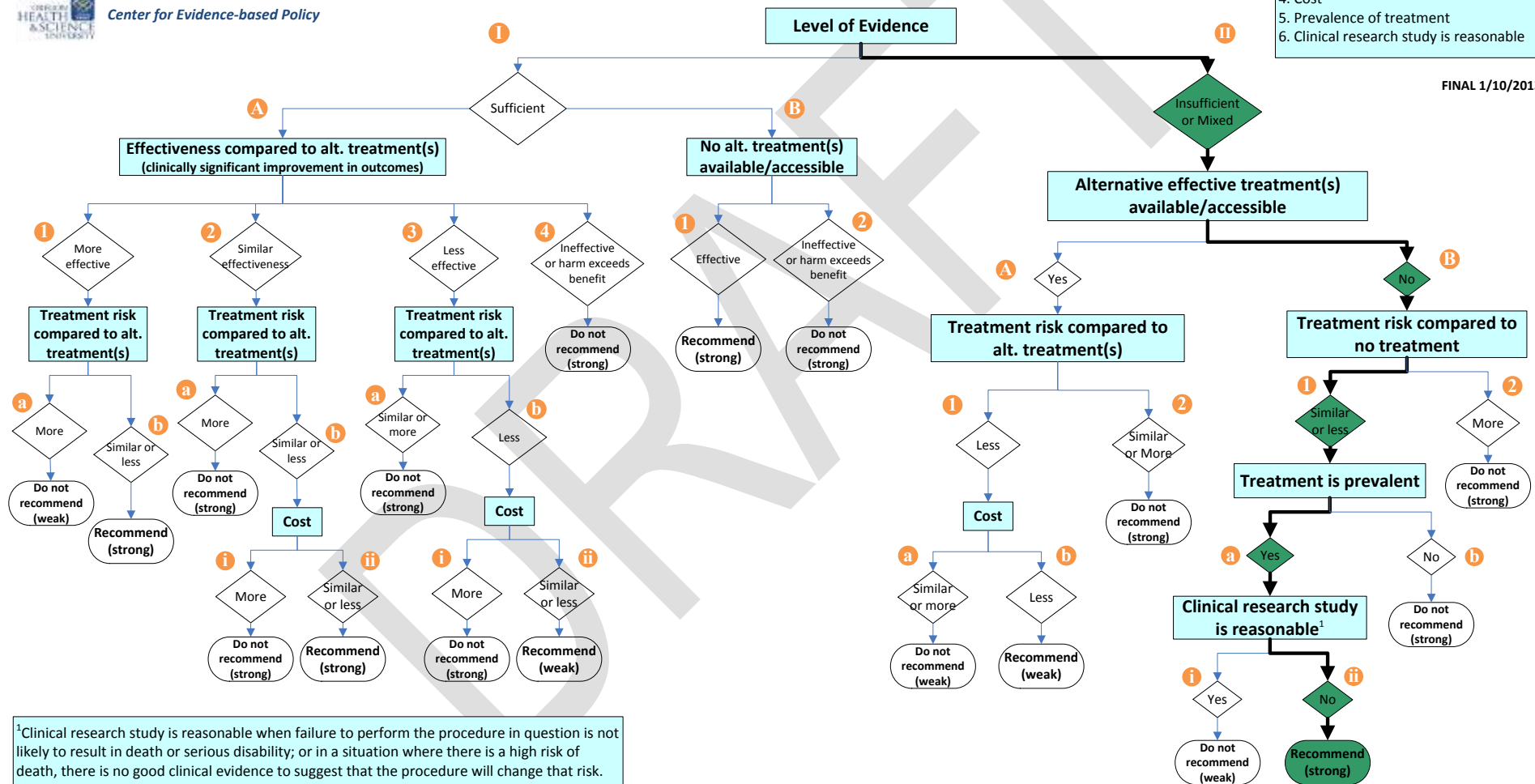
HERC Guidance Development Framework

Refer to HERC Guidance Development Framework Principles for additional considerations

Decision Point Priorities

1. Level of evidence
2. Effectiveness & alternative treatments
3. Harms and risk
4. Cost
5. Prevalence of treatment
6. Clinical research study is reasonable

FINAL 1/10/2013



Appendix D. Grading Systems

Tonnis Classification of Osteoarthritis by Radiographic Changes

Grade 0: No signs of osteoarthritis (OA)

Grade 1: Increased sclerosis of femoral head or acetabulum, slight joint space narrowing or slight slipping of joint margin, no or slight loss of head sphericity

Grade 2: Small cysts in femoral head or acetabulum, moderate joint space narrowing, moderate loss of head sphericity

Grade 3: Large cysts, severe joint space narrowing or obliteration of joint space, severe deformity of the head, avascular necrosis

Outerbridge grades include the following:

Grade 0: Normal

Grade I: Cartilage with softening and swelling

Grade II: Partial-thickness defect with fissures on the surface that do not reach subchondral bone or exceed 1.5 cm in diameter

Grade III: Fissuring to the level of subchondral bone in an area with a diameter more than 1.5 cm

Grade IV: Exposed subchondral bone head

HERC Coverage Guidance – Hip Surgery Procedures for Femoroacetabular Impingement (FAI) Syndrome

Disposition of 2nd Round of Public Comments

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Commenters

Identification	Stakeholder
A	<i>American Association of Orthopaedic Surgeons (AAOS), Washington, D.C.</i>
B	<i>Smith & Nephew, Inc., Andover, MA</i>
C	<i>Arthroscopy Association of North America, Rosemont, Illinois</i>
D	<i>Andrea Herzka, MD, Assistant Professor, Dept. of Orthopaedic Surgery and Rehabilitation, OHSU, Portland, OR</i> HERC Appointed Expert

HERC Coverage Guidance – Hip Surgery Procedures for Femoroacetabular Impingement (FAI) Syndrome

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A	1	Thank you for the opportunity to comment on the draft guidance regarding hip surgery procedures for Femoroacetabular Impingement Syndrome (FAI). The American Association of Orthopaedic Surgeons (AAOS) represents 98% of the orthopaedic surgeons practicing in the United States, 368 of whom practice in Oregon. Orthopaedic surgeons are the preeminent physicians providing medical treatment of musculoskeletal conditions and disease. The AAOS firmly supports the incorporation of evidence into clinical practice, and is actively involved in developing and promoting Evidence Based Clinical Practice Guidelines for a number of musculoskeletal conditions. However, the AAOS opposes the proposed “no coverage” determination put forth by the Health Evidence Review Commission (HERC), because we do not believe this decision is consistent with evidence showing that surgery is a cost-effective treatment for the management of FAI Syndrome. Surgical treatment of FAI for symptomatic patients with ongoing disability issues can provide long- lasting symptom relief and allows these patients to return to work or other desired activities, reducing FAI’s economic burden on society.	Thank you for this information.
A	2	The American Medical Association (AMA) concluded that FAI surgery is clinically effective; granting three Category 1 CPT codes effective January 2011. One criterion for granting Category 1 CPT codes is that “the clinical efficacy of the service/procedure is well established and documented in U.S. peer reviewed literature.” The AAOS believes that if a service or procedure has a Category I CPT code, it is not experimental or investigational. Therefore, payers should not deny reimbursement for these services and procedures when they are medically necessary. When payers do otherwise, they threaten the health of the public and unjustifiably interfere with the physician/patient relationship.	The existence of a Category I CPT code is not sufficient evidence of effectiveness.
A	3	All national U.S. commercial insurers and Medicare cover FAI surgery because it has been shown to be clinically effective. Since 2008, six independent systematic reviews of FAI surgery have concluded that published evidence supports its safety and effectiveness.	The HTAS is aware of this, but does not reach its conclusions based on the decisions of other payers. References not provided.
A	4	More than 40 peer-reviewed publications for symptomatic FAI using arthroscopic, open, or a combination of these surgical approaches report that patients’ symptoms are relieved and they are able to return to their normal activity levels.	References not provided. HTAS is unaware of any studies that were not included in the WA HTA report that are not case series. Case series are highly susceptible to bias and a lower quality type of evidence. However, given the large volume of studies with favorable results, and the likelihood of significant delay in conducting a RCT, HTAS has recommended coverage of surgical correction. Relates to discussion question #1

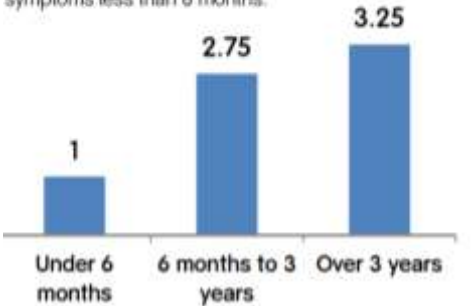
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A	5	In July 2011, the National Institute for Health and Clinical Excellence in the United Kingdom stated in published guidance on open and arthroscopic FAI surgery, that current evidence of the efficacy of the procedures is adequate for the relief of associated symptoms.	HTAS is aware of the NICE guidance and it is included in the coverage guidance document. Their guidance acknowledges little or no controlled data comparing the procedure with other interventions or natural history. The structure of healthcare delivery in the UK allows them to create a registry to track outcomes. HTAS has elected a similar recommendation, despite the inability to require the use of a registry. Relates to discussion question #1
A	6	The AAOS once again urges the Committee to revise its coverage guidance on hip surgery procedures for Femoroacetabular Impingement Syndrome (FAI) to be consistent with the other evidence-based coverage determinations and provide access to this safe, effective, and cost-effective treatment to Oregon's public employees and Oregon Health Plan participants. Thank you for your consideration of these comments. Please do not hesitate to contact AAOS if we can be of further assistance.	HTAS has recommended coverage of surgical correction of FAI syndrome.
B	7	Smith & Nephew, Inc. is a global medical technology business specializing in Endoscopy, Orthopedics and Wound Management. We comment on the draft coverage guidance for surgery for Femoroacetabular Impingement (FAI) posted June 27, 2013. FAI understanding is evolving. Recognition of FAI as a disorder is a process in evolution. About 70 percent of all the literature on FAI has been published in 2010 or later. (Figure 1) Unrecognized, and/or inappropriately managed symptomatic FAI can lead to inefficient and wasteful use of medical resources. ¹	Thank you for taking the time to comment. HTAS is aware that a large volume of literature has been published since the date of the WA HTA report, but is unaware of any study type other than case series or retrospective cohort studies that were not included in that review (see comment #4). Despite this fact, given the large volume of studies with favorable results, and the likelihood of significant delay in conducting a RCT, HTAS has recommended coverage of surgical correction of FAI syndrome.

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		Figure 1. Number of Publications on FAI (PubMed) (as of July 5, 2013)  <table><caption>Data for Figure 1: Number of Publications on FAI (PubMed)</caption><thead><tr><th>Year</th><th>Number of Publications</th></tr></thead><tbody><tr><td>1999</td><td>1</td></tr><tr><td>2000</td><td>0</td></tr><tr><td>2001</td><td>3</td></tr><tr><td>2002</td><td>3</td></tr><tr><td>2003</td><td>5</td></tr><tr><td>2004</td><td>10</td></tr><tr><td>2005</td><td>18</td></tr><tr><td>2006</td><td>27</td></tr><tr><td>2007</td><td>45</td></tr><tr><td>2008</td><td>41</td></tr><tr><td>2009</td><td>87</td></tr><tr><td>2010</td><td>101</td></tr><tr><td>2011</td><td>147</td></tr><tr><td>2012</td><td>168</td></tr><tr><td>2013</td><td>154</td></tr></tbody></table>	Year	Number of Publications	1999	1	2000	0	2001	3	2002	3	2003	5	2004	10	2005	18	2006	27	2007	45	2008	41	2009	87	2010	101	2011	147	2012	168	2013	154	
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2009	87																																		
2010	101																																		
2011	147																																		
2012	168																																		
2013	154																																		
B	8	Pre-operative diagnosis. Contrary to the Health Technology Assessment published by Washington State, FAI can reasonably be diagnosed with high probability.¹⁻⁴	• Refs #1 and 2 were published before the date of the WA HTA report (last search date June 2011). The HTAS bases their guidance documents on reviews of the literature that utilize the highest standards of evidence based medicine. Studies are included or excluded based on transparent, reproducible criteria; therefore the HTAS does not investigate individual studies. The HTAS assumes that the conclusions reached by the authors of these reviews weigh all the available evidence in accordance with the principles of evidence based medicine, and does not attempt to re-review the entire body of evidence to reach its own conclusions. • Ref #3 is a SR of arthroscopic treatment of FAI. Authors report “We found that there was great inconsistency among the indications for arthroscopic management of FAI. Clinical and radiographic indices remain largely unvalidated.” • Ref #4 is a SR of treatment of FAI using open surgical dislocation. Authors state: “In short, there were major inconsistencies in the reported clinical and radiographic criteria used to indicate surgery among the 15 studies reviewed.” and “These results showed that that there																																

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			was an inconsistency between the clinical and radiographic indications for surgical hip dislocation as a treatment for femoroacetabular impingement.” Both of these reviews appear to contradict the commenter’s statement.								
B	9	Risk of delaying treatment for FAI. A recent evaluation of 561 consecutive hip arthroscopy patients (574 procedures: labral tear, 60.8%; FAI, 22.6%; condylar lesions, 16.6%) evaluated three patient segments by duration of symptoms: less than six months, six months to three years and over three years. Repeat arthroscopy on the same side or revision were more common in patients with delayed surgery⁵ (Figure 2). Figure 2. Hip Arthroscopy in 561 patients Relative risk of revision hip arthroscopy or arthroplasty on same side compared to patients with symptoms less than 6 months.  <table border="1"><thead><tr><th>Duration of Symptoms</th><th>Relative Risk</th></tr></thead><tbody><tr><td>Under 6 months</td><td>1</td></tr><tr><td>6 months to 3 years</td><td>2.75</td></tr><tr><td>Over 3 years</td><td>3.25</td></tr></tbody></table>	Duration of Symptoms	Relative Risk	Under 6 months	1	6 months to 3 years	2.75	Over 3 years	3.25	This is a consecutive case series that compares outcomes based on length of symptoms. From abstract, unclear what kinds of baseline differences existed between groups, and whether they were controlled for. Relates to discussion question #4
Duration of Symptoms	Relative Risk										
Under 6 months	1										
6 months to 3 years	2.75										
Over 3 years	3.25										
B	10	Philippon et.al. reported professional hockey players who delayed surgery beyond one year after acute injury were significantly slower in returning to sport.⁶ Patients without access to joint preservation surgery who have unremitting symptomatic FAI may be left with total hip replacement as the only next step alternative.	The citation was published before the date of the WA HTA report (last search date June 2011) (see comment #8).								
B	11	Diagnostic recognition. The American Medical Association concluded FAI surgery was clinically effective and granted three Category Level 1 CPT codes effective January 2011.	See comment #2								
B	12	The United Kingdom’s National Institute for Health and Clinical Excellence (NICE) released guidance in September 2011 and July 2011, respectively, on arthroscopic and open surgery for FAI stating published evidence is adequate that surgery in symptomatic patients results in short- and medium-term benefits.^{7,8}	See comment #5								
B	13	Health technology appraisals from all national commercial insurers recommend coverage in patients	No TA available on the TEC website. Citation is a medical								

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		with symptoms and documented inability to participate in desired activities. Regence Blue Cross/Blue Shield covering Oregon, completed and published a Health Technology Assessment of FAI surgery in February 2013 and recommends it as “medically necessary to debride the bone when specific criteria are met.” ⁹	coverage policy from BCBS, not a TA. Evidence review methods not specified and quality of review unknown. Evidence in the policy is summarized as follows: • Not all patients with FAI morphology will have FAI pathology. • There is a high association between FAI pathology and idiopathic osteoarthritis, but this may represent a small proportion of the total cases of hip osteoarthritis. • Patients may present with hip pain that can be diagnosed as FAI by a combination of clinical evaluation, radiographs, and MR arthrography. • In cases in which there is a positive impingement test result, anterosuperior labral or acetabular damage identified on MR arthrography and a pistol-grip morphology identified on imaging, there is a very high probability that the acetabular damage is caused by impingement of the femoral head-neck junction against the acetabular rim. FAI can be verified intraoperatively. • Repair of the labrum alone can improve symptoms in the short term. It is reasonable to expect that debridement/osteoplasty of the bump or bone spur would reduce continued abrasion in the long term. Some studies, albeit of low quality, support this view. • Treatment of FAI is most effective in younger patients without osteoarthritis (Tonnis grade 0 or I) or severe cartilage damage. Although osteoarthritis can be identified with plain film radiographs, articular damage is not always identified with current imaging techniques. • There is a high probability that symptoms in patients with osteoarthritis (Tonnis grade II or III, or joint space of less than 2 mm) or severe cartilage damage (Outerbridge grade IV) will not improve following osteoplasty. These patients may require THA for progressing pain within 5 years.

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			- In large case series, arthroscopic treatment of FAI in young to middle-age patients without osteoarthritis and showing mild to moderate cartilage damage results in 75% to 85% of patients improved. - Smaller case series suggest that open treatment of FAI in young to middle-age patients with moderate to severe cartilage damage results in 50% to 70% of patients improved. Non-union has been reported to occur in 27% of patients following the transection of the great trochanter with hip dislocation. The literature is uncertain with respect to the following: - It is not known whether arthroscopic or open approaches result in better net health outcomes when patients are matched for severity of FAI morphology and articular cartilage damage. - It is not known which patients with FAI morphology are most likely to progress to osteoarthritis. The progression of pincer impingement with damage initially restricted to the labrum may follow a different time course than cam-type impingement. - It is not known whether treatment of FAI will reduce the occurrence of osteoarthritis. HTAS has recommended coverage of surgical correction of FAI syndrome with medical necessity criteria. Relates to discussion question #6
B	14	Conservative management is ineffective. A just published systematic review reports, “Outcomes of operative treatment of femoroacetabular impingement are significantly better than nonsurgical management.”¹⁰ Non-surgical treatment of symptomatic FAI does not provide permanent symptom relief, may require permanent lifestyle modification and fails to allow patients to return to desired activity levels.^{6;11-28}	Ref #10 (Harris 2013) is a SR that includes 29 studies, overall quality score was poor. All study types with a minimum 2 year FU were eligible for inclusion. 83% were case series, total N=2369. While the author reports statistics to support the superiority of operative over non-operative treatment, there was only one study of non-operative management, which was a case

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			series with n=37. No direct comparative evidence is reported. • Ref #6, 11-25 and 27 were published before the date of the WA HTA review (see comment #8). • Ref #26 is a case series of 23 patients evaluating the use of a specific hip distractor in the OR rather than a traction table. • Ref #28 is a retrospective case series of 47 high level athletes who underwent arthroscopic treatment of FAI. There was a 30% loss to follow up. The evaluable patients had significant improvements in pain (17/100 points) and function (12/100 points) scores (generally accepted minimum clinically important difference for HHS is 10). Relates to discussion question #2
B	15	Surgery relieves symptoms and allows patients to return to activity. Over 46 peer-reviewed publications for symptomatic FAI using arthroscopic, open or a combination of these surgeries report patients' symptoms are relieved and the majority of patients are capable of returning to their previous level of activity.^{6;11-13;15-21;23;26-62} <u>There are no unfavorable reports.</u> Arthroscopic surgery for FAI was associated with the lowest overall risk of complications. Among these publications, 21 reports with collectively over 1300 patients document favorable surgical outcomes in 75 to 100 percent of symptomatic FAI patients who had failed non-surgical management comprised of medication, reduced activity and physical therapy or rehabilitation programs lasting up to and over one-year. Typical patients have been able to return to recreational and work activities within months and professional athletes have had their careers extended.^{6;11-15;17-23;26-28;45;53;55;58;61}	Minimum Clinically Important Difference (MCID) has not been defined according to the WA HTA report for either mHHS or NASH. • Refs #6-23, 27, 29-52 and 56 were published before the date of the WA HTA review (see comment #8). • For Ref #26 and 28, see comment #14. • Ref #53 is another case series of 200 athletes, median improvement in MHHS was 20 points. • Ref #54 is a retrospective cohort study comparing labral repair with labral resection, and reported more improvement in those undergoing labral repair. • Ref #55 is a case series of 100 treated arthroscopically, median improvement was 21 points. • Ref #57 is a case series of 120 treated with minimally invasive anterolateral approach. Mean improvement in non-arthritis hip score (NASH) was 32 points. • Ref #58 is a case series of 44 athletic patients treated with the mini-open approach. Mean HHS improved 24 points.

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			- Ref #59 is case series of 185/233 hips with 5 year FU treated with surgical hip dislocation. 82% were satisfied with the surgery. 14 hips underwent THA or major revision. - Ref #60 is SR that includes 31 studies of “generally low methodologic quality” and concludes “arthroscopy, open surgery and arthroscopic surgery followed by mini open surgery are comparable for functional results, biomechanics, and return to sport. Debridement and osteoplasty provide better results than debridement only. Significantly improved outcomes have been recorded in patients undergoing labral refixation than resection.” - Ref #61 is case series of 60 patients < age 17. Mean improvement in MHHS was 34. 13% required a second surgery for adhesions. - Ref #62 is a case series of 153 patients > age 50. 20% required THA (time period not clear). HTAS has recommended coverage of surgical correction of FAI syndrome. Relates to discussion question #1
B	16	Since 2008, seven independent systematic reviews of FAI surgery for symptomatic patients each concluded that published evidence support its safety and effectiveness. ^{10;63-68} Additional favorable reports have subsequently been published. ^{17;28;53;54;57-62}	- For Ref #10, see comment #14. - Ref #17 and 63-68 were published before the date of the WA HTA report (see comment #8). - For Refs #28, 53, 54 and 57-62, see comment #15.
B	17	FAI surgery is reported to be cost-effective. In a cost-effectiveness analysis⁶⁹ based upon best available data for patients with symptomatic FAI, observation or arthroscopic repair followed by hip replacement is compared to an endpoint of delaying total hip replacement surgery. FAI surgery was determined to be very cost-effective by the definition of cost-effectiveness used by the World Health Organization. It was more likely to demonstrate value in patients with limited pre-existing osteoarthritis or if progression to end-stage osteoarthritis is delayed.	Ref #69 is a CEA that reports an ICER of \$21,700 assuming a 3 year benefit of arthroscopy and no impact of treatment on natural history (no delay of progression to OA). Relates to discussion question #5
B	18	FAI surgery is right for patients with unremitting symptomatic FAI.	All referenced citations were published before the date of

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		FAI may be asymptomatic in many patients and all patients with FAI may not progress to osteoarthritis in the short-term. Additionally, outcomes are less favorable in the presence of preexisting advanced osteoarthritis of the affected hip. 6;11;20;29;30;46;70;71	the WA HTA report (see comment #8).
B	19	HERC solicited orthopedic expert Dr. Andrea Herzka to review the evidence. She stated on the Expert Review Form submitted April 22, 2013, "...parameters for medical necessity must be established to allow this population to receive the current standard of care for FAI which is arthroscopic intervention." The strong recommendation your guidance proposes to not cover FAI surgery is contrary to the conclusions from the best available evidence, your expert reviewer, Medicare and commercial insurers. Failure to cover hip surgeries for FAI will prevent patients who are suffering from chronic pain and disability from access to a surgery unanimously found reasonable, safe, effective and medically necessary. Patients with unremitting pain from symptomatic FAI and no hip preservation surgery option may ultimately seek hip replacement, a more costly alternative. We urge you to act in the best interest of your patients and cover FAI surgery in symptomatic patients meeting appropriate criteria.	HTAS is aware of Dr. Herzka's opinion, as she has provided both oral and written testimony to the committee on two occasions. HTAS has recommended coverage of surgical correction of FAI syndrome.
C	20	The Arthroscopy Association of North America (AANA) is an Accredited Council for Continuing Medical Education approved organization which exists to promote, encourage, support and foster, through continuing medical education functions, the development and dissemination of knowledge in the discipline of surgery. This is done to improve upon the diagnosis and treatment of diseases and injuries of the musculoskeletal system to enhance the lives our patients. AANA has 3691 members across the United States, Canada and Mexico dedicated to this mission. We are recognized internationally as leaders in teaching the management of musculoskeletal disease states and have been using evidence based methodologies to support that teaching for over 30 years. We welcome the recent trend toward more evidence based practice that the Oregon Health Authority has adopted. AANA works closely with the American Academy of Orthopedic Surgeons in formulating Clinical Practice Guidelines and Appropriate Use Criteria to assist orthopedic surgeons in providing treatment recommendation that incorporate the best available evidence in the medical literature.	Thank you for your comment and your interest in evidence based practice.
C	21	The recent recommendation published for comment by the Health Technology Assessment Subcommittee (HTAS) of the Oregon State Health Evidence Review Commission (HERC) on the surgical treatment of femoroacetabular impingement (FAI) troubles us. We believe it violates the tenets of evidence based medicine and the currently recognized standard of care for patients with symptomatic FAI in the Oregon medical community as well as nationally. Evidence based medicine seeks to improve patient care by 1) using clinical expertise, 2) searching the scientific literature for the best available studies to evaluate and compare treatments, and 3)	Ref #1 also states "It is when asking questions about therapy that we should try to avoid the non-experimental approaches, since these routinely lead to false positive conclusions about efficacy. Because the randomized trial, and especially the systematic review of several randomized trials, is so much more likely to inform us and so much less likely to mislead us, it has become the "gold standard" for judging whether a treatment does more

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		include patient values and preferences in recommending therapies. ¹ The HERC has severely limited the inclusion of all the medical evidence that supports the surgical treatment of FAI, discounted expert clinical opinion, and not included at all the aspect of patient preferences in its strong recommendation against coverage for these procedures.	good than harm.” Relates to discussion question #1
C	22	There are only two evidence sources cited for the recommendation; the Washington State Healthcare Authority Technology Assessment ² and the National Institute for Health and Clinical Excellence (NICE) ³ both from 2011. The WSCH HTA severely circumscribed evidence synthesis rules to favor randomized clinical trials (RCT) as demonstration of procedure efficacy. This methodology ignores the over 40 peer-reviewed case-controlled and case series publications demonstrating improved outcomes from FAI surgery in symptomatic patients that this young, active population of patients experiences when conservative care fails. By stressing RCTs as the only measure of clinical efficacy, the HERC does not allow for a true assessment of the surgical literature as it exists today, limiting patient access to important therapies.	The WA HTA report is a full systematic review. It is unclear what the commenter means by “WSCH HTA severely circumscribed evidence synthesis rules to favor randomized clinical trials (RCT) as demonstration of procedure efficacy.” The tenets of evidence-based medicine are clear that, in general, RCTs are required to draw valid conclusions, because to do otherwise results in significant propensity for bias. Indeed, nearly all Cochrane reviews limit their inclusion criteria to RCTs. However, given the large volume of studies with favorable results, and the likelihood of significant delay in conducting a RCT, HTAS has recommended coverage of surgical correction. Relates to discussion question #1
C	23	The NICE report actually states, “Current evidence on the efficacy of femoro–acetabular surgery for hip impingement syndrome is adequate in terms of symptom relief in the short and medium term.” ³ The NICE recommendation cited does not justify a strong recommendation against covering these procedures.	See comment #5 Relates to discussion question #1
C	24	A recent high quality review of the surgical treatment of FAI not included in the HTAS review states, “Outcomes of operative treatment of femoroacetabular impingement are significantly better than nonsurgical management. Surgical treatment significantly improves outcomes, with no consistent significant differences exhibited between open and arthroscopic techniques. Open surgical dislocation has significantly greater reoperation and complication rates vs. mini-open and arthroscopic techniques. Outcomes of labral refixation are significantly better than debridement in patients with labral injuries.” ⁴	This is the same SR (Harris 2013) previously addressed in comment #14. Relates to discussion question #2 Relates to discussion question #6
C	25	As recognized experts in the treatment of these conditions, the members of AANA consider the surgical treatment of symptomatic FAI to be <i>the standard of care</i> ⁵ for those patients that fail the conservative management of these conditions. The HTAS recommendation against coverage violates this standard and places these patients at unnecessary risk of further pain, disability and potentially irreversible joint destruction. ^{6,7} Since FAI surgery is recognized as a standard, there is no clinical equipoise ⁸ to support conducting RCTs. Indeed, “If the clinician knows, or has good reason to believe,	HTAS disagrees that there is no clinical equipoise, however, given the large volume of studies with favorable results, and the likelihood of significant delay in conducting a RCT, HTAS has recommended coverage of surgical correction.

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		that a new therapy (A) is better than another therapy (B), he cannot participate in a comparative trial of Therapy A versus Therapy B. Ethically, the clinician is obligated to give Therapy A to each new patient with a need for one of these therapies.” ⁹	Relates to discussion question #3 Relates to discussion question #4
C	26	Lastly, Medicare and private insurers do cover surgery for FAI ¹⁰ . To deny coverage to patients for these procedures who are covered by Oregon State creates a potential treatment disparity for the poor and minority patients served by state programs such as Medicaid.	HTAS is aware of the coverage policies of other payers (see comment #3).
C	27	Evidence based methodologies are necessary to help improve patient care and make treatment more consistent with the current state of medical knowledge. It is important to have experts examine guidelines to offer necessary insight concerning their relevance and veracity. The members of AANA hope that you will reconsider your coverage decision to avoid the standard of care and treatment disparity issues we have described. We would be happy to advise the HERC on further guidelines concerning musculoskeletal healthcare to improve the care that all the citizens of Oregon deserve.	HTAS has recommended coverage of surgical correction of FAI syndrome.
D	28	The proposed draft for coverage for FAI is outdated and flawed. The literature used to create this draft comprised of articles published prior to 2011. More recent citations that I provided to the committee have not yet been incorporated into this guideline. Although the level of evidence of many outcome studies is level IV, their cumulative value is powerful. The safety and efficacy of hip arthroscopy for FAI associated non arthritic hip pain is well established.	None of the evidence previously submitted provides direct comparison between operative and non-operative management. However, given the large volume of studies with favorable results, and the likelihood of significant delay in conducting a RCT, HTAS has recommended coverage of surgical correction. Relates to discussion question #1
D	29	A specific example of the inaccuracy of the proposed draft is the statement that there is no evidence to support one surgical treatment over another when Dr. Larson, Dr. Philippon and Dr. Ganz have both published that labral preservation results in significantly improved outcomes. As the expert on FAI for the state of Oregon, I cited several articles relevant to this guideline and published since the Washington State Health Care Authority Health Technology Assessment Program recommendation in early 2011.	Several cohort studies were provided previously that suggest differences in efficacy based on surgical technique, as reported in the Harris SR (see comment #14). The WA HTA report concludes the there is no evidence that one specific treatment, including surgical approach, results in better outcomes. HTAS does not believe the evidence is strong enough at the time to limit coverage of the procedure to one particular technique.
D	30	I provided a powerpoint presentation and strongly encouraged the subcommittee to create a category for medical necessity that would allow for coverage for this disabled patient population after failed conservative treatment and when all other criteria for medical necessity have been met. This is an effective way to allow disabled patients to have access to newer technologies when there are no known alternative treatment options.	HTAS has recommended coverage of surgical correction of FAI syndrome with medical necessity criteria. Relates to discussion question #6
D	31	The authors also state that proponents of surgery for FAI “believe that surgical correction of the	Thank you for this clarification regarding the current

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		impinging deformities will alleviate the symptoms and retard the progression of osteoarthritis degeneration.” This is incorrect. The current literature supports surgical intervention for patients with symptomatic FAI refractory to conservative treatment. The surgical goal is pain reduction and improved function. These outcomes measures have been successfully reproduced and documented in short and midterm outcome studies. The safety and efficacy of surgical intervention for FAI is very well documented. In patients with refractory non-arthritis hip pain due to FAI related chondrolabral care surgical intervention is the current standard of care. We are hopeful that long term data will <i>also</i> demonstrate a change in the natural history and retardation of arthritic progression, but at this time this data remains unknown. For this reason, FAI surgery is not indicated as a prophylactic surgery in individuals without significant disability and pain. The uncertainty of the natural history or the impact of surgery on arthritic progression is irrelevant to this guidance recommendation. This outcome measure can not be known for several years, but the efficacy of pain reduction and improved function and level of activity are outcome measures that are well documented in short and mid term outcome studies.	indications for surgical intervention.
D	32	The algorithm used by the commission is incorrect. Under “alternative effective treatments available” the committee chooses “yes.” I am unaware of any alternative effective treatment options for FAI related non arthritic hip pain in patients refractory to conservative treatment. My patients have all failed a combination of physical therapy, massage, steroid injections, acupuncture, chiropractic care, heat, ice, NSAIDS, and at times opiates prior to surgical intervention.	Thank you for providing your opinion on this matter. HTAS agrees that this service should be covered only for those who have failed all other treatment options. Relates to discussion question #2
D	33	Nonarthritic hip pain associated with FAI can be debilitating. Many young patients are unable to walk, sit or perform their job duties. When conservative treatment fails in this patient population, surgical intervention becomes a matter of medical necessity. BCBS, aetna, Tricare, healthnet, lifewise, MODA, pacificsource, cigna, and providence insurance carriers have all updated their coverage guidelines for FAI based on the literature to cover surgery when “medical necessity” criteria are met. Although these criteria differ very slightly from one another, they are conceptually identical. The Washington State Health Care Authority Health Technology Assessment Program is the only group of reviewers to determine a non-coverage guideline and this was based on literature through the latter part of 2010. It is the only review to date that denies its patients of the current standard of care for the treatment of FAI.	HTAS is aware of the coverage policies of other payers (see comment #3). Relates to discussion question #4
D	34	The data for FAI supports the following progression through the current HERC algorithm. Alternative treatment avail?- NO Treatment risk compared to no treatment- similar or less (difficult to quantify chronic pain and loss of function, weight gain due to inactivity and the cost of unemployment, obesity, depression and	<i>HTAS agrees and has changed its recommendation for coverage.</i> Relates to discussion question #3 Relates to discussion question #4

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Ident.	#	Comment	Disposition
		chronic pain) but the minor known risks of FAI surgery seem to outweigh the consequences of untreated pain Treatment is prevalent- YES – covered by all commercial insurance carriers and performed in every European country, Canada, Mexico, and Brazil, Korea, and Japan. Clinical research study is reasonable- NO	
D	35	Patients who have already failed months of PT and activity modification should not be subjected to further lack of intervention. The orthopedic surgery societies are all in agreement that denial of surgical intervention after failed conservative treatment is not ethical given the profound disability that these patients suffer.	HTAS has recommended coverage of surgical correction of FAI syndrome with medical necessity criteria. Relates to discussion question #3
D	36	Certainly research to better understand the efficacy of conservative treatment of FAI is warranted. Those patients who have not trialed any conservative therapy should be studied, but unfortunately, this population might not be well represented in the orthopedic literature because the majority of patients who present to my office have already failed a course of PT and are desperate for pain relief. The primary care and/or physical therapy providers will likely need to conduct this type of study since they are likely treating patients with FAI associated pathology successfully with PT. Those patients rarely make it to my office and their exclusion creates a bias. In addition, patients successfully treated with PT often cancel follow up since they are improved. Finding a primary care practice with a high enough volume of FAI patients with hip pain to study prospectively is a huge hurdle to research. Capturing this patient population is extremely difficult and we will never know how many patients with mild pain self treat successfully with activity modification.	Thank you for clarifying that FAI can be treated conservatively with PT. HTAS has recommended coverage of surgical correction of FAI syndrome after failure of a trial of PT and other conservative management. Relates to discussion question #2 Relates to discussion question #3
D	37	Prospective evaluation of conservative treatment of FAI is challenging for the reasons explained above. For this reason, I have recommended that the subcommittee uses the algorithm to make a strong “yes” recommendation for the surgical treatment of FAI associated non arthritic hip pain in patients with symptoms refractory to conservative treatment. Those few patients whom I see in my office who have not trialed a formal course of PT with avoidance of flexion and focus on strengthening are treated initially with this conservative care. If treatment fails after 3-6 months, then surgery is recommended. It is my experience that a minority of patients are successfully managed without surgery, and that increased activity level/athleticism and younger age are associated with high failure rate of conservative care. Lastly, the subcommittee wanted to know how patients with this condition have been managed historically prior to this intervention. Many patients had to live with “a bum wheel.” They could no longer go for a walk with friends, sit or stand at their jobs, or have sex without severe pain. These patients were often told “there was nothing wrong” because their X-rays did not demonstrate	Thank you for providing your opinion on this matter. HTAS has recommended coverage of surgical correction of FAI syndrome with medical necessity criteria. Relates to discussion question #2

HERC Coverage Guidance – Hip Surgery Procedures for Femoroacetabular Impingement (FAI) Syndrome

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Ident.	#	Comment	Disposition
		arthritis and nobody could explain this elusive groin pain. These patients lived with chronic pain and fear of hip rotation and flexion. Without an explanation for their pain they likely suffered both physically and emotionally.	
D	38	Dr. Ganz, the first surgeon to describe FAI came to this concept after performing hundreds of hip replacements in young patients with premature advanced arthritis and years of preceding pain with similarly misshapen hips. This finding guided his philosophy that this abnormal morphology caused painful injuries to the cartilage and labrum in the hip joint and led to eventual arthritis: thus, the introduction of the concept of FAI.	Thank you for this information.

HERC Coverage Guidance – Hip Surgery Procedures for Femoroacetabular Impingement (FAI) Syndrome Disposition of 2nd Round of Public Comments

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D	None (references submitted previously)

HERC Coverage Guidance – Hip Surgery Procedures for Femoroacetabular Impingement (FAI) Syndrome

Disposition of 2nd Round of Public Comments

Appendix A: Discussion Questions & Relevant Comments

(Used to guide discussion during 9/23/13 HTAS Meeting)

1. Is the very low quality evidence sufficient to recommend coverage?

NICE and Washington HTA differed on the sufficiency of the evidence, with NICE finding it weak but sufficient for coverage with a registry. Many commenters believe case series evidence to be sufficient. See comments ([4](#), [5](#), [15](#), [21](#), [22](#), [23](#), [28](#))

2. Are alternative effective treatments available/accessible for persons with FAI?

Expert comment indicates physical therapy is sufficient for some (but not all) patients with FAI-related hip pain, but no evidence was reviewed regarding the effectiveness of physical therapy or other nonsurgical alternatives for those who do not benefit from physical therapy. See comments ([14](#), [24](#), [32](#), [36](#), [37](#))

3. Is conducting a higher-quality study reasonable despite prevalence of treatment?

Expert testimony is that a randomized trial is not reasonable due to prevalence of the treatment. See comments ([25](#), [34](#), [35](#), [36](#))

4. What is the risk compared to alternative/no treatment?

Commenters describe risk of significant disability for patients who fail to benefit from physical therapy and do not have FAI surgery. However, surgery includes some risk of complications. See comments ([9](#), [25](#), [33](#), [34](#))

5. How do cost, along with patient values and preferences, affect the subcommittee's decision after reviewing the evidence?

Commenters cite the disabling nature of this condition, and its effects on younger patients which could result in high costs to society and patient preference for surgery. See comments ([17](#))

6. If the subcommittee chooses to recommend coverage, what are the appropriate indications for surgery? Should the subcommittee recommend coverage for resection and repair, or just repair?

See comments ([13](#), [24](#), [29](#))

7. Comments Designated for HTAS Discussion

See comments ([6](#), [13](#), [15](#), [19](#), [21](#), [27](#), [30](#), [31](#), [32](#), [34](#), [37](#))

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

Line 133

When using 314.9, Unspecified Hyperkinetic Syndrome, in children age 5 and under, it is appropriate only when the following apply:

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

First line therapy is "parent-behavior training" (i.e. Triple P (Positive Parenting of Preschoolers) Program, Incredible Years Parenting Program, Parent-Child Interaction Therapy and New Forest Parenting Program). The term "parent" refers to the child's primary care givers, regardless of biologic or adoptive relationship.

Second line therapy is pharmacotherapy.

Use of 314.9 for children age five and younger is limited to pairings with the following procedure codes with first and second line therapy as denoted above:

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

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN

DRAFT for VbBS Meeting Materials 10/10/2013

HERC COVERAGE GUIDANCE

Children under Age 6

For children under 6 diagnosed with disruptive behavior disorders¹, including those at risk for ADHD, specific parent behavior training² is recommended for coverage as first-line therapy (*strong recommendation*).

Pharmacotherapy³ is recommended for coverage as a second line therapy (*weak recommendation*).

Provider consultation with teachers is recommended for coverage (*weak recommendation*).

Children Age 6 and Over

For children 6 and over who are diagnosed with ADHD¹, pharmacotherapy³ alone (*weak recommendation*) or pharmacotherapy³ with psychosocial/behavioral treatment (*strong recommendation*) are recommended for coverage.

Provider consultation with teachers is recommended for coverage (*weak recommendation*).

¹*Children with comorbid mental health conditions may require additional or different treatments that are not addressed in this guidance.*

²*Effective studied types of parent behavior training include: Triple P (Positive Parenting of Preschoolers) Program, Incredible Years Parenting Program, Parent-Child Interaction Therapy and New Forest Parenting Program. The term "parent" refers to the child's primary care givers, regardless of biologic or adoptive relationship.*

³*Limited to medications that are FDA-approved for the condition.*

Note: Definitions for strength of recommendation are provided in Appendix A GRADE Element Description

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Health Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

EVIDENCE SOURCE

American Academy of Pediatrics (AAP). (2011). Supplemental information. Implementing the key action statements: An algorithm and explanation for process of care for the evaluation, diagnosis, treatment, and monitoring of ADHD in children and adolescents. *Pediatrics*, SI1-SI21. Retrieved December 5, 2012, from <http://pediatrics.aappublications.org/content/128/5/1007/suppl/DC1>

Charach, A., Dashti, B., Carson, P., Booker, L., Lim, C.G., Lillie, E., et al. (2011). *Attention deficit hyperactivity disorder: Effectiveness of treatment in at-risk preschoolers; long-term effectiveness in all ages; and variability in prevalence, diagnosis, and treatment. Comparative effectiveness review no. 44.* (Prepared by the McMaster University Evidence-based Practice Center under Contract No. MME2202 290-02- 0020.) AHRQ Publication No. 12-EHC003-EF. Rockville, MD: Agency for Healthcare Research and Quality. Retrieved from www.effectivehealthcare.ahrq.gov/reports/final.cfm.

The summary of evidence in this document is derived directly from these evidence sources, and portions are extracted verbatim.

SUMMARY OF EVIDENCE

Clinical Background

Attention deficit hyperactivity disorder (ADHD) is a condition characterized by inattention, overactivity, and impulsivity. While ADHD can begin before children enter

school, it is most commonly identified and treated in primary school. Boys are classified with ADHD approximately twice as frequently as girls, and primary school-age children approximately twice as frequently as adolescents. ADHD symptoms exist on a continuum in the general population and are considered a “disorder” to a greater or lesser degree. Symptoms are clinically significant when they cause impaired functioning. The DSM-IV criteria include subtypes: (1) predominantly inattentive, (2) predominantly hyperactive-impulsive, and (3) combined inattentive and hyperactive.

Although the condition now classified as ADHD was first described clinically in 1902, few treatments were available until the 1950s, when methylphenidate (brand name, Ritalin) was developed to target the condition. The use of pharmacotherapy has increased through the years, along with refinements in understanding and recognition of the condition as a disorder. The diagnosis of ADHD and prescriptions for its treatment have grown exponentially, particularly in North America. By the end of the 1960s, approximately 150,000 to 200,000 children were treated with stimulants, which represented 0.002% of the U.S. child population at that time. In contrast, the U.S. National Survey of Child Health provides a 2003 estimate of 4.4 million children who were identified at some point as having ADHD, which represents 7.8% of that population, of which 2.5 million (56%) were receiving medication. Within the United States, the estimated prevalence of adult ADHD stands at 4.4%. Prescriptions for the treatment of ADHD have increased as well, with methylphenidate prescriptions increasing from 4 million to 11 million, and prescriptions for amphetamines increasing from 1.3 million to 6 million in an eight year period of time (1991-1999).

Drugs currently FDA approved for treatment of ADHD and their maximum recommended daily dosages are listed in Table 1. In addition, a variety of antidepressants are used off-label to treat this condition.

Table 1. FDA Approved Medications for the Treatment of ADHD

Drug Class/ Generic name	Brand names	FDA Approved max dose/day
<i>Amphetamine preparations</i>		
Mixed amphetamine salts	Adderall	40mg
	Adderall XR	30mg
Dextroamphetamine	Dexedrine, Dextrostat	40mg
	Dexedrine spanule	40 mg
Lisdexamfetamine	Vyvanse	70mg
<i>Methylphenidate preparations</i>		
Dexmethylphenidate	Focalin	20mg

Drug Class/ Generic name	Brand names	FDA Approved max dose/day
	Focalin XR	30mg
Methylphenidate HCL	Methylin, Ritalin, Ritalin LA, Ritalin SR, Metadate CD, Metadate ER	60mg
	Daytrana	30mg
	Concerta	54mg < 13 years/ 72mg ≥ 13 years ¹
SNRIs		
Atomoxetine	Strattera	1.4mg/kg or 100mg
Other		
Guanfacine extended release	Intuniv	4mg
Clonidine extended release	Kapvay	0.4mg/day

Evidence Review

The purpose of this review is to critically examine the effectiveness and adverse events of interventions in preschool children with clinically significant disruptive behavior and therefore at high risk for ADHD and to similarly examine the comparative long-term effectiveness and adverse events of interventions for ADHD.

Treatment of Preschoolers with Disruptive Behavior Disorders

For the management of preschoolers with disruptive behavior disorders, including children considered to be at risk for ADHD², evidence was grouped into two broad categories of treatment: behavioral interventions and psychostimulant medication. A total of 31 studies evaluated parent behavior training, which was primarily defined as one of four manualized programs³. Nearly all studies showed positive effects, and pooled results for eight good-quality studies also found a significant improvement in

¹ From AAP 2011 reference

² The ADHD diagnosis has not been widely applied in children under age 6 because of uncertainty regarding the reliability and validity of the diagnostic criteria in this age group. Because ADHD in this age group is commonly identified in the context of other disruptive behaviors, and in children with diagnoses of Disruptive Behavior Disorders including Oppositional Defiant Disorder and Conduct Disorder, the evidence review includes studies of children less than six with Disruptive Behavior Disorders.

³ Triple P (Positive Parenting of Preschoolers) Program, Incredible Years Parenting Program, Parent-Child Interaction Therapy and New Forest Parenting Program

child behavior with parent behavior training. In addition, the single good-quality study of methylphenidate finds that it appears to be effective. The strength of evidence for use of parent behavior training was judged high due to number of studies and consistency of results. The strength of evidence for methylphenidate was judged low because there is only one good-quality study.

Long-term extension (follow-up) studies for the RCTs of parent behavior training suggest that the benefits are maintained for several years, although no long-term study (lasting 12 months or more) of parent behavior training alone included untreated comparison groups, and attrition was high. A recent study examining parent behavior training with and without school-based teacher or child interventions included a no-treatment control. This study showed maintenance of benefits of parent behavior training at two years. Studies do not comment on adverse events related to parent behavior training.

Five studies examining combinations of parent behavior training and school or daycare interventions for preschool children at risk for disruptive behavior disorder and/or ADHD suggest that adding classroom teacher consultation may be important for children in low socioeconomic status (SES) communities, but not for families with educated parents who live in communities with resources, although direct comparisons of identical interventions offered to families of different SES have not yet been performed. All behavioral interventions showed benefits relative to no-treatment controls, and a dose response to the number of parent behavior training sessions attended by parents was also identified, enhancing the overall strength of evidence for effectiveness of parent behavior training.

Several small, short-term trials of psychostimulant medication use in preschoolers, primarily immediate release methylphenidate, suggest that it is efficacious and safe. In addition, the Preschool ADHD Treatment Study (PATs), a large, high quality trial funded by the National Institute of Mental Health also suggests that methylphenidate is effective for improving parent-rated child behavior in preschoolers. This multisite trial had multiple phases, beginning with 10 sessions of parent behavior training. The training was followed by an open label safety lead-in phase of a psychostimulant medication, then a titration phase, a cross-over phase and open-label maintenance phase that lasted 10 months. The PATs study offers information about both the potential benefits and limitations of stimulant medication use in very young children. Limitations include the following: preschool children experience more dose-related adverse events than older children, stimulants interfere with rates of growth, and the presence of three or more comorbid conditions and psychosocial adversity are associated with lessened effectiveness of psychostimulant medication. These findings are supported by two additional “fair” quality RCTs.

In conclusion, both parent behavior training and psychostimulant medication are effective treatment for preschoolers with disruptive behavior disorders. There are no adverse events reported for parent behavior training, while there are adverse effects with methylphenidate. This favors the use of parent behavior training for preschoolers at risk for ADHD due to disruptive behavior. A direct comparison has not yet been done.

Long-Term Effectiveness and Safety of Interventions in People Age 6 and Older

Pharmacologic Agents

The long-term effectiveness and safety (at least 12 months of treatment and/or follow up) of several psychostimulants (e.g., methylphenidate immediate release amphetamine, Osmotic-controlled Release Oral delivery System methylphenidate, dextroamphetamine, mixed amphetamine salts, atomoxetine, clonidine and guanfacine extended release) have all been examined prospectively in children and adolescents age 6 and over. The agents examined were all shown to be efficacious for control of inattention, overactivity, and impulsiveness for at least 12 months and up to three years, and few serious adverse events were noted, although guanfacine extended release appears to be less well tolerated than other agents examined. Global ratings of impairment also indicate continued benefit throughout the extension studies for patients still receiving medications. In general, those who remain on medication show continued benefit, and few adverse events are reported for them. With a majority of the studies funded by industry (12 of 21), there may be enhanced representations of effectiveness and safety. Psychostimulants continue to provide control of ADHD symptoms and are well tolerated for months to years at a time.

Fewer children experienced adverse events with methylphenidate than with dextroamphetamine. Concerns about adverse events led to discontinuation of medications for 15% to 20% of children age 6 and over using extended release mixed amphetamine salts. Concerns about exacerbation of tics with stimulants appear to be unfounded, although the sample size remains small. Use of psychostimulants slows the rate of growth, and increases blood pressure and heart rate to a small degree. At a group level, the mean changes are clinically insignificant, although on rare occasions individuals discontinue an agent because of changes in vital signs. There are many similarities between methylphenidate immediate release and other preparations of psychostimulants, both in terms of efficacy and in the side effect profile. Therefore, many researchers and clinicians assume all psychostimulants are effective and safe for extended periods of time. The documentation for this assertion is not yet robust.

Atomoxetine is both safe and effective for ADHD symptoms over 12 to 18 months among children and for up to three years in adults. Discontinuation in children and teens appears to be higher (26%) due to ineffectiveness and lower (3%) due to adverse events than with other agents, although these are not direct comparisons. As with

psychostimulants, the group means for blood pressure and heart rate show small but clinically insignificant increases. There is only one study of a pharmacologic intervention over an extended time period (three years) in adults with ADHD, and that study found symptom improvement was maintained for those on atomoxetine, and discontinuation due to adverse events was somewhat higher for adults (11%) than for children (3%).

An extension study of guanfacine suggests that this agent is also effective in controlling ADHD symptoms for up to two years; however, high rates (40% to 60%) of somnolence, headache, and fatigue occur when it is used as a monotherapy, especially in the initial six to eight months of treatment. A second study examined concurrent use of psychostimulants and noted improved tolerance to these adverse effects. Changes in vital signs occur, but no clear group trends are noted. Individuals may develop clinically significant hypotension and bradycardia. Serious adverse events include syncope and clinically significant changes on electrocardiogram.

Overall, pharmacologic agents used for controlling the symptoms of inattention, overactivity, and impulsivity of ADHD show maintenance of effectiveness and safety for 12 to 24 months. Following that, attrition from use interferes with the ability to draw conclusions. Along with decreased symptoms, overall functioning is improved.

Psychosocial and Behavioral Interventions, Alone and in Combination with Medication
Investigations comparing psychosocial/behavioral interventions, alone and in combination with psychostimulant medication management, showed that both medication and combined medication/behavioral treatment (including school-based interventions) are more effective in treating ADHD and oppositional defiant disorder symptoms than psychosocial or behavioral interventions alone. Psychosocial interventions in the four included trials included intensive behavioral treatment (parent behavior training, child-focused treatment and a school-based intervention), multimodal treatment (parent behavior training, behavior management training, family therapy and child social skills training), “behavior treatment” (undefined) and EEG biofeedback.

Longer Term Outcomes

Evaluation of long-term outcomes (five or more years follow up) following interventions for ADHD is complex due to multiple patterns of services used and very few studies available, with only two RCTs of well-characterized clinical samples, both of boys ages 7 to 9 years with DSM-IV ADHD, combined subtype. The best quality data come from the Multimodal Treatment of ADHD Study, which compared 14 months of management with immediate release methylphenidate to three other interventions: psychosocial and behavioral treatment; the combination of medication management and psychosocial and behavioral treatment; and standard community care. Three years after initiation, the four intervention groups showed comparable outcomes. No clear relationship was identified between duration of medication use and psychiatric or overall functional outcomes at

three years or beyond. In contrast, a few long-term cohort studies lasting five years or more suggest that increased duration of medication was associated with improved grade retention and academic achievement. No prospective studies have been designed to investigate the question of long-term functional outcomes directly. There appear to be long-term academic benefits with medication interventions in some domains.

In conclusion, the evidence for long-term effectiveness of pharmacologic agents for improving ADHD symptoms is based on a single good study for methylphenidate and a single good study for atomoxetine. These studies followed the children for 12 or 14 months and showed benefit with few adverse effects, thereby resulting in low strength of evidence for longer term effectiveness for each of these agents. Similarly, there is a single good study showing benefits for the combination of methylphenidate and psychosocial interventions. The evidence for other pharmaceutical agents is insufficient, as is the evidence pertaining to parent behavior training and academic interventions.

[\[Evidence Source\]](#)

Evidence Summary

For children under age six, both parent behavior training and psychostimulant medication are effective treatment for preschoolers with disruptive behavior disorders. Classroom teacher consultations in addition to parent behavior training are beneficial to children of lower socioeconomic status. There are no adverse events reported for parent behavior training, while there are adverse effects with methylphenidate.

In children age six and over, there is evidence to support the long-term effectiveness of both methylphenidate and atomoxetine for improving ADHD symptoms, as well as methylphenidate combined with behavioral/psychosocial interventions. There is evidence for only the short-term effectiveness for other FDA approved medications and guanfacine, the latter of which has more frequent adverse events.

GRADE-INFORMED FRAMEWORK

The HERC develops recommendations by using the concepts of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for carrying out the steps involved in developing recommendations. There are four elements that determine the strength of a recommendation, as listed in the table below. The HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Balance between desirable and undesirable effects, and quality of evidence, are derived from the evidence presented in this document, while estimated relative costs, values and preferences are assessments of the HERC members.

Indication	Balance between desirable and undesirable effects	Quality of evidence	Resource Allocation	Values and preferences	Coverage Recommendation
Pharmacologic treatment age <6	net benefit, despite some harms	low	modest costs	likely moderate variability in parent preferences for treatment	Pharmacotherapy is recommended for coverage as a second line therapy (<i>weak recommendation</i>)
Parent Behavior Training (PBT) age <6	net benefit without apparent harms	high	modest costs	likely moderate variability in parent preferences for treatment	Specific parent behavior training is recommended for coverage as first-line therapy (<i>strong recommendation</i>)
Behavioral/ psychosocial treatment age <6 (excluding PBT)	no evidence	insufficient	modest costs	likely moderate variability in parent preferences for treatment	<i>No recommendation</i>
Pharmacologic treatment alone and combined with behavioral/ psychosocial interventions age ≥ 6	net benefit, despite some harms	low	modest costs	likely moderate variability in parent preferences for treatment	Pharmacotherapy alone (<i>weak recommendation</i>) or pharmacotherapy with psychosocial/ behavioral treatment (<i>strong recommendation</i>) are considered first-line therapy and are recommended for coverage

Indication	Balance between desirable and undesirable effects	Quality of evidence	Resource Allocation	Values and preferences	Coverage Recommendation
Behavioral/ psychosocial treatment alone, PBT, academic interventions age ≥ 6	unable to draw conclusions	insufficient	modest costs	likely moderate variability in parent preferences for treatment	Behavioral/ psychosocial treatment alone, PBT, academic interventions age ≥ 6 for primary ADHD are not recommended for coverage (<i>weak recommendation</i>)
School/ daycare based interventions	net benefit in those <6 of low SES, benefit in ≥ 6 as element of intensive behavioral treatment, no apparent harms	low	modest costs	likely minimal variability in parent preferences	School/daycare based interventions are outside the purview of this coverage guidance (<i>No recommendation</i>) Provider consultation with teachers is recommended for coverage (based on evidence of children <6 with low SES) (<i>weak recommendation</i>)

*The Quality of Evidence rating was assigned by the primary evidence source, not the HERC Subcommittee

Note: GRADE framework elements are described in Appendix A

POLICY LANDSCAPE

Five quality measures were identified when searching the [National Quality Measures Clearinghouse](#). The Institute for Clinical Systems Improvement developed three measures around diagnosis and management of attention deficit hyperactivity disorder (ADHD) in primary care for school age children and adolescents: 1) Percentage of patients diagnosed with ADHD whose medical record contains documentation that the clinician discussed the need for school-based supports and educational service options for children with ADHD; 2) Percentage of patients treated with psychostimulant medication for the diagnosis of ADHD whose medical record contains documentation of a follow-up visit at least twice a year; and 3) Percentage of patients newly diagnosed with ADHD whose medical record contains documentation of DSM-IV-TR or DSM-PC criteria. These three measures have not been endorsed by the National Quality Forum (NQF).

The National Committee for Quality Assurance developed two HEDIS measures, which are both endorsed by the NQF: 1) Follow-up care for children prescribed ADHD medication (initiation phase): percentage of members 6 to 12 years of age with an ambulatory prescription dispensed for ADHD medication, who had one follow-up visit with a practitioner with prescribing authority during the 30-day initiation phase; and 2) Follow-up care for children prescribed ADHD medication (continuation and maintenance [C&M] phase): percentage of members 6 to 12 years of age with an ambulatory prescription dispensed for ADHD medication, who remained on the medication for at least 210 days and who, in addition to the visit in the initiation phase, had at least two follow-up visits with a practitioner within 270 days (9 months) after the initiation phase ended.

Oregon's Coordinated Care Organizations' quality of care objectives include the following measure: Meet or exceed the 90th percentile national Medicaid benchmarks for follow up care for children on ADHD medication.

COMMITTEE DELIBERATIONS – EVIDENCE-BASED GUIDELINE SUBCOMMITTEE

The Evidence-based Guidelines Subcommittee had extensive deliberations on the types and availability of behavioral and psychology treatments available. An additional literature search was performed to determine if additional types of interventions had evidence to support beyond the parent behavioral training, and none were found. The decision was also made to remain silent on the treatment of children over 6 with behavioral treatments alone, due to implementation considerations. Subcommittee members determined the best way to address the coordination with teachers for school-based interventions was through communication/coordination between the provider and teacher being recommended as a covered service.

COMMITTEE DELIBERATIONS – VALUE-BASED BENEFITS SUBCOMMITTEE

The VbBS approved the draft coverage guidance and updated its guideline note on ADHD at its meeting 8/8/2013.

Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

Appendix A. GRADE Framework Description

Element	Description
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Costs (resource allocation)	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted

Strong recommendation

In Favor: The subcommittee is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Against: The subcommittee is confident that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Weak recommendation

In Favor: the subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Against: the subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Quality of evidence across studies for the treatment/outcome

High = Further research is very unlikely to change our confidence in the estimate of effect.

Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low = Any estimate of effect is very uncertain

Appendix B. Applicable Codes

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
312.9	Unspecified disturbance of conduct
314	Hyperkinetic syndrome of childhood
314.0	Attention deficit disorder of childhood
314.00	Attention deficit disorder without mention of hyperactivity
314.01	Attention deficit disorder with hyperactivity
314.1	Hyperkinesis with developmental delay
314.2	Hyperkinetic conduct disorder
314.8	Other specified manifestations of hyperkinetic syndrome
314.9	Unspecified hyperkinetic syndrome
ICD-9 Volume 3 (Procedure Codes)	
None	
CPT Codes	
90785	Interactive complexity, add-on code to be used in conjunction with codes for primary service
90791	Psychiatric diagnostic evaluation (no medical services)
90792	Psychiatric diagnostic evaluation (with medical services)
90832	Psychotherapy, 30 minutes with patient and/or family member
90834	Psychotherapy, 45 minutes with patient and/or family member
90837	Psychotherapy, 60 minutes with patient and/or family member
90839	Psychotherapy for crisis, first 60 minutes
90840	Add-on for each additional 30 minutes of psychotherapy for crisis, used in conjunction with code 90839
90845	Psychoanalysis
90846	Family psychotherapy without the patient present
90847	Family psychotherapy, conjoint psychotherapy with the patient present
90849	Multiple-family group psychotherapy
90853	Group psychotherapy (other than of a multiple-family group)
90863	Pharmacologic management, including prescription and review of medication, when performed with psychotherapy services; used only as add-on to primary psychotherapy code
98960	Education and training for patient self-management by a qualified, nonphysician health care professional using a standardized curriculum, face-to-face with the patient (could include caregiver/family) each 30 minutes; individual patient
98961	2-4 patients
98962	5-8 patients
HCPCS Codes	
H2027	Psychoeducational service, per 15 minutes
S9444	Parenting classes, non-physician provider, per session
S9482	Family stabilization services, per 15 minutes
T1027	Family training and counseling for child development, per 15 minutes

Note: Inclusion on this list does not guarantee coverage

Appendix C. HERC Guidance Development Framework – ADHD Indications

Pharmacologic Treatment age <6 as 1st Line Therapy



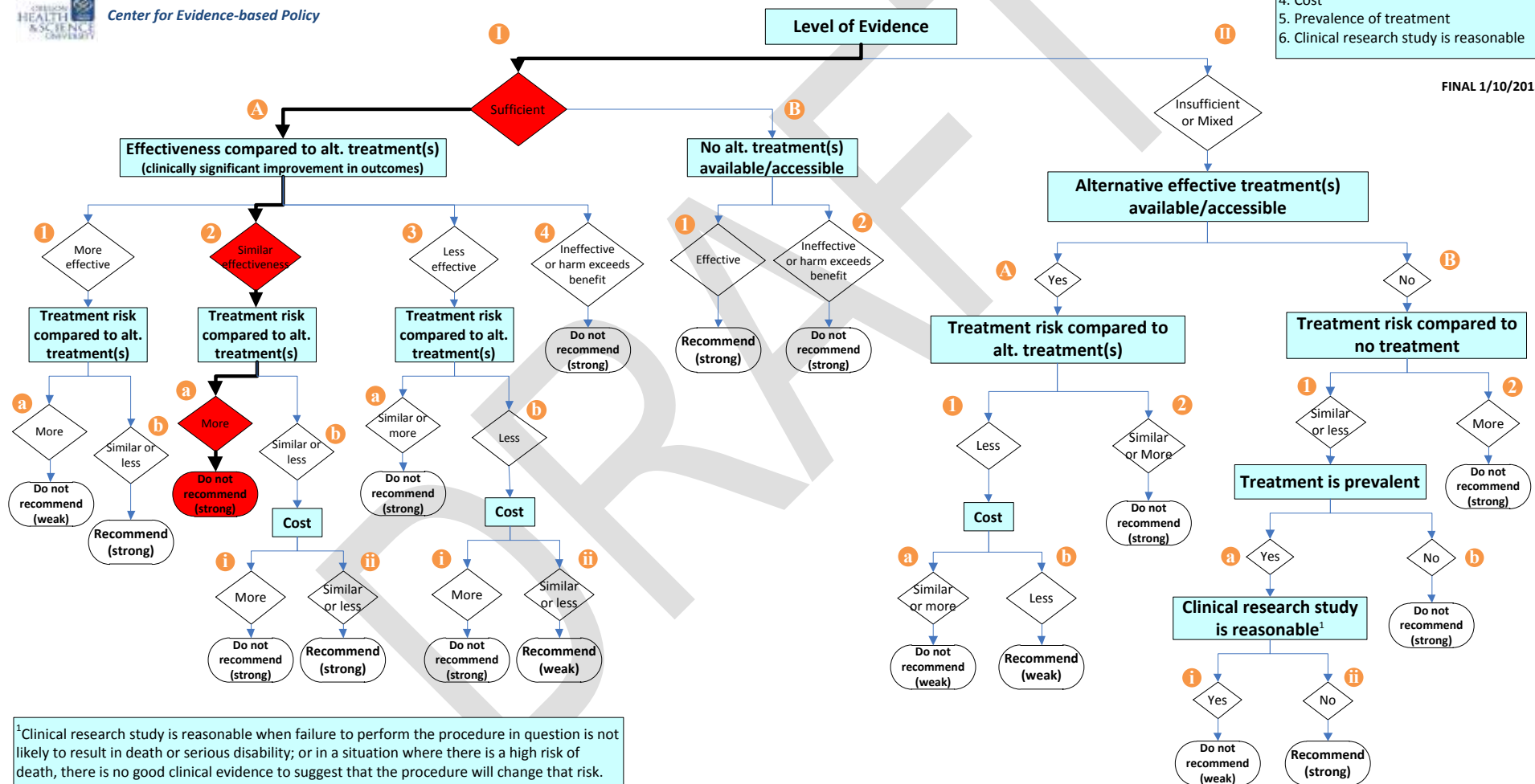
Center for Evidence-based Policy

HERC Guidance Development Framework

Refer to *HERC Guidance Development Framework Principles* for additional considerations

- Decision Point Priorities**
1. Level of evidence
 2. Effectiveness & alternative treatments
 3. Harms and risk
 4. Cost
 5. Prevalence of treatment
 6. Clinical research study is reasonable

FINAL 1/10/2013



Pharmacologic Treatment age <6 as 2nd Line Therapy



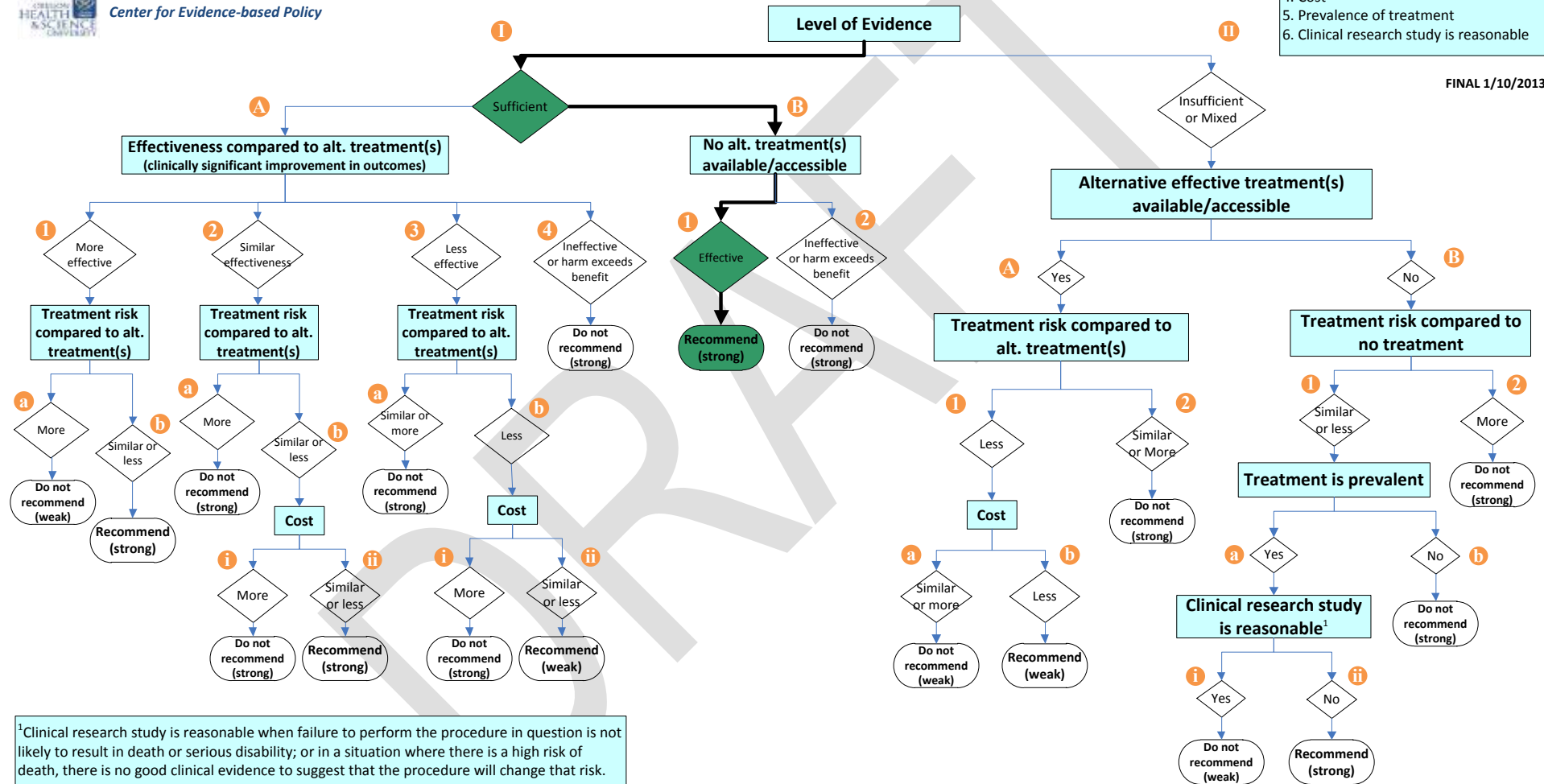
Center for Evidence-based Policy

HERC Guidance Development Framework

Refer to HERC Guidance Development Framework Principles for additional considerations

- Decision Point Priorities**
1. Level of evidence
 2. Effectiveness & alternative treatments
 3. Harms and risk
 4. Cost
 5. Prevalence of treatment
 6. Clinical research study is reasonable

FINAL 1/10/2013



Parent Behavior Training (PBT) or School/Daycare Interventions age <6 Compared to Pharmacologic Treatment

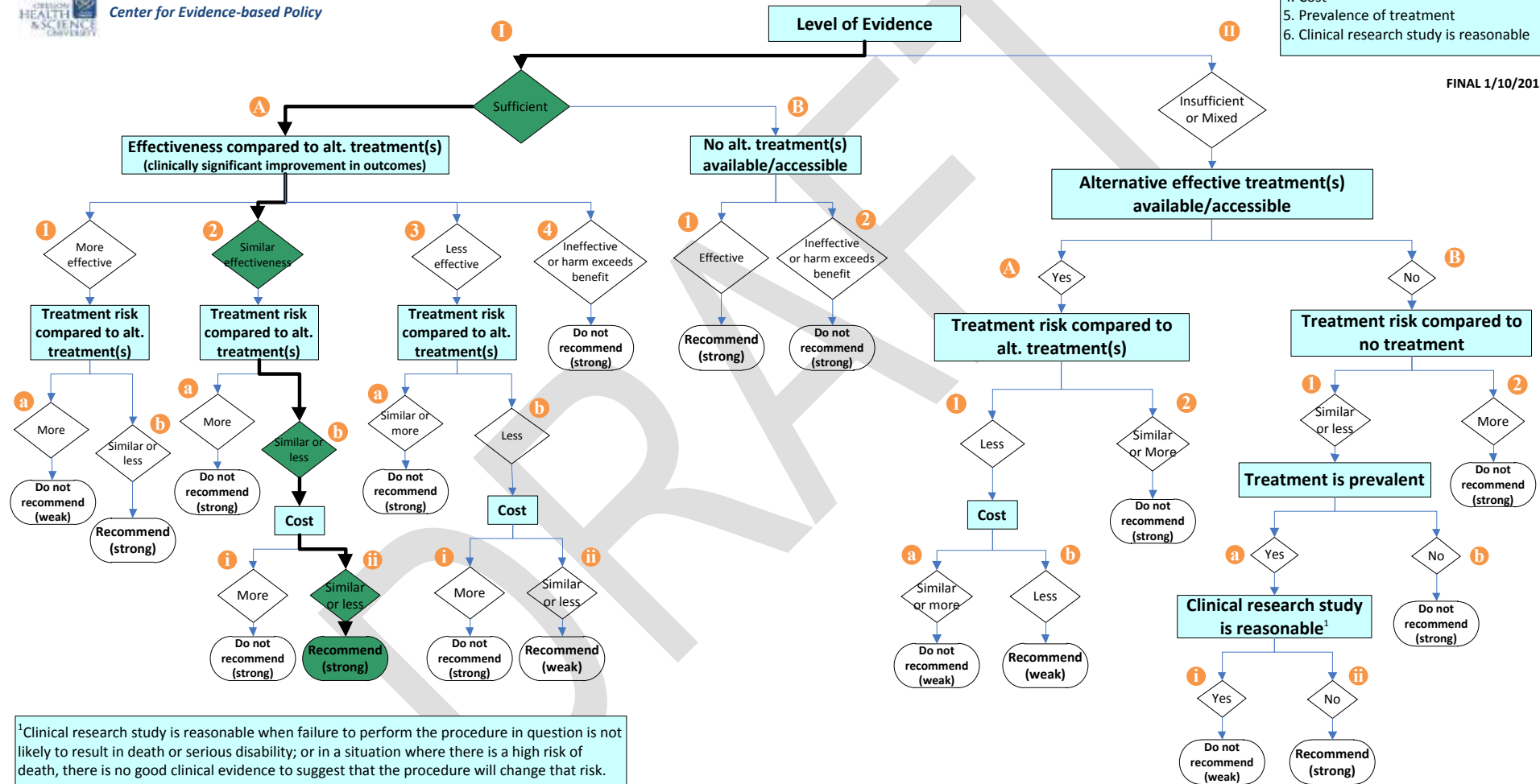


HERC Guidance Development Framework

Refer to HERC Guidance Development Framework Principles for additional considerations

- Decision Point Priorities**
1. Level of evidence
 2. Effectiveness & alternative treatments
 3. Harms and risk
 4. Cost
 5. Prevalence of treatment
 6. Clinical research study is reasonable

FINAL 1/10/2013



Pharmacologic Treatment Alone and Combined with Behavioral/Psychosocial Interventions Age ≥ 6



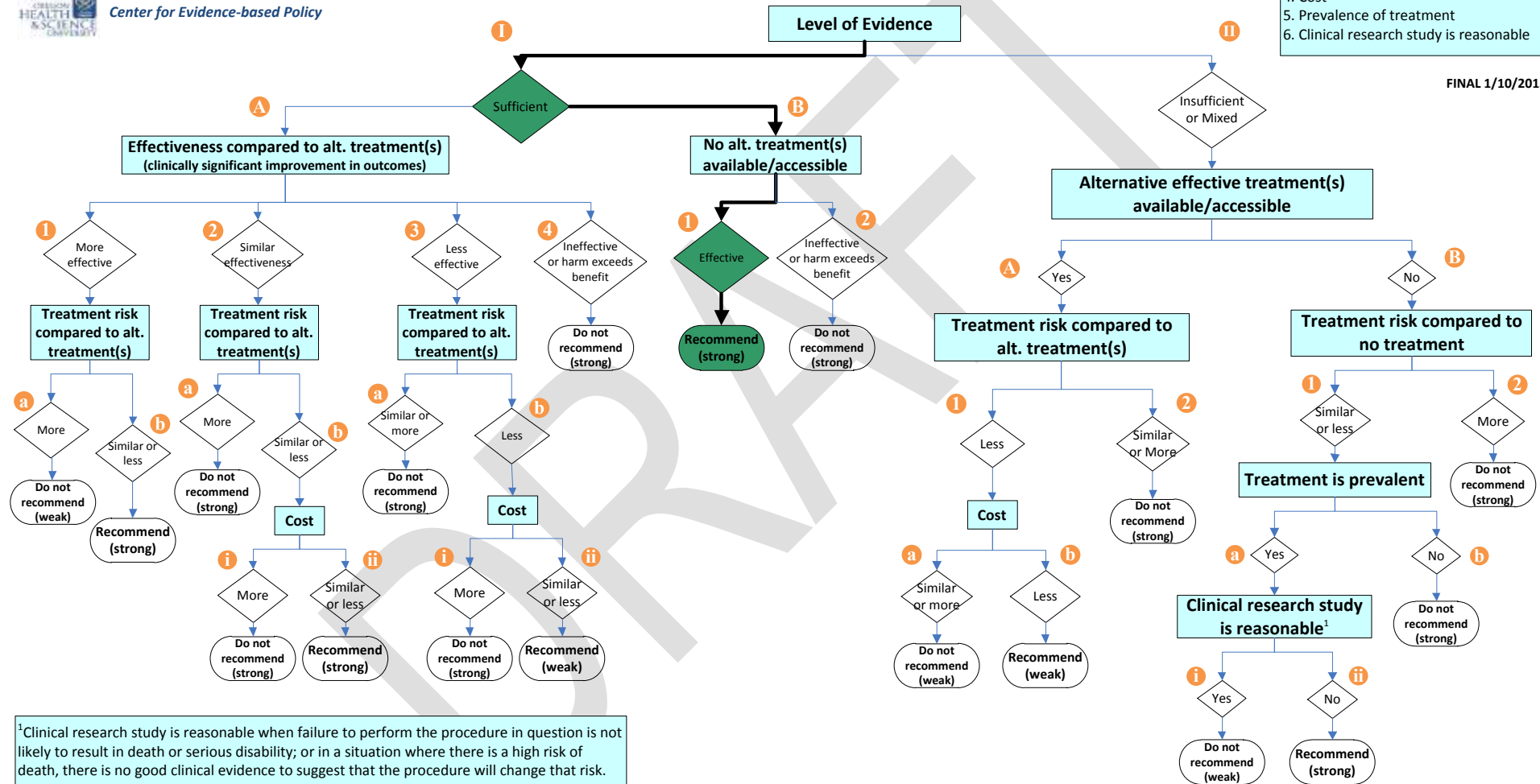
Center for Evidence-based Policy

HERC Guidance Development Framework

Refer to HERC Guidance Development Framework Principles for additional considerations

- Decision Point Priorities**
1. Level of evidence
 2. Effectiveness & alternative treatments
 3. Harms and risk
 4. Cost
 5. Prevalence of treatment
 6. Clinical research study is reasonable

FINAL 1/10/2013



¹Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

Behavioral/Psychosocial Treatment Alone, PBT, Academic Interventions Age ≥ 6 Compared to Pharmacologic Treatment

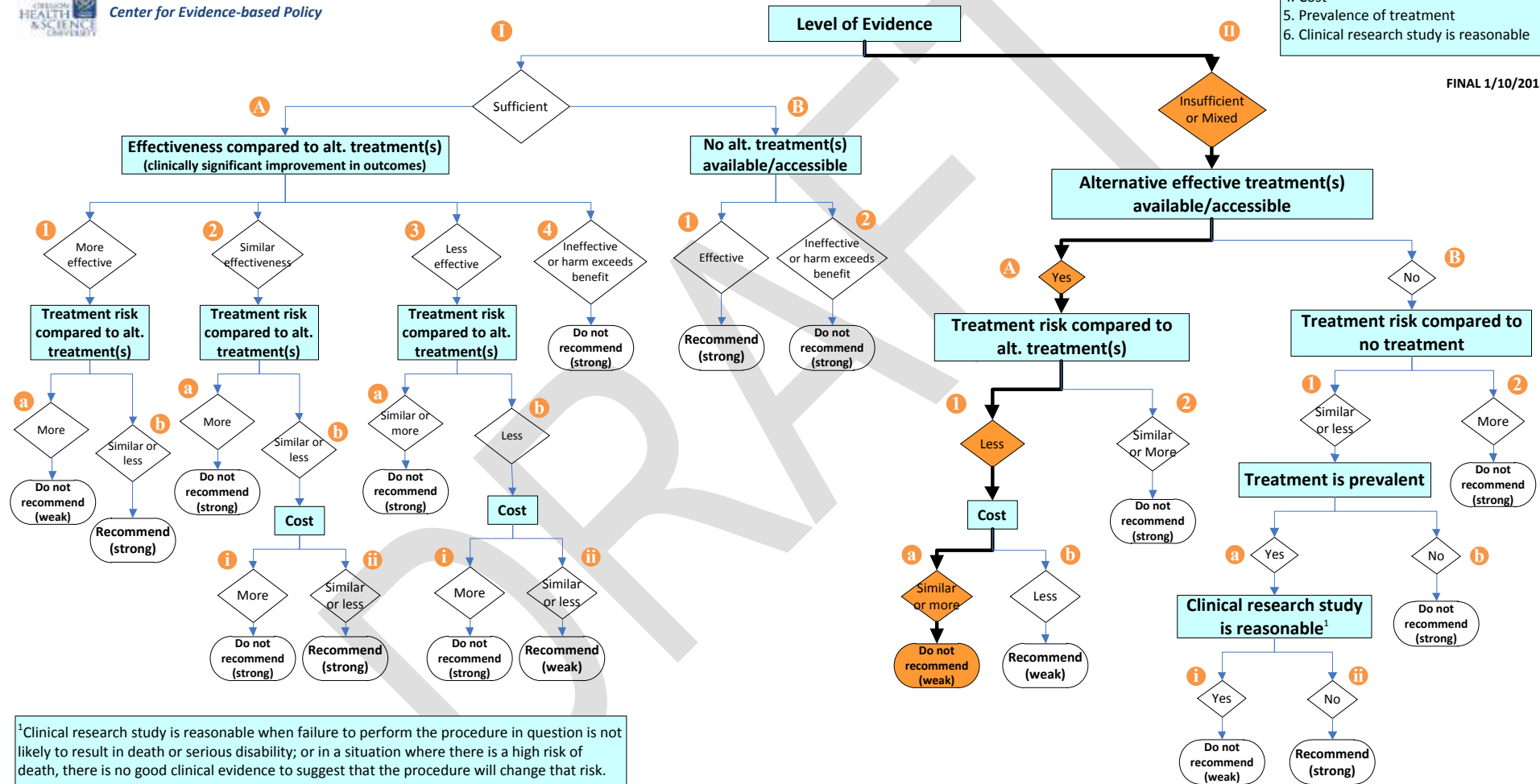


HERC Guidance Development Framework

Refer to *HERC Guidance Development Framework Principles* for additional considerations

- Decision Point Priorities**
1. Level of evidence
 2. Effectiveness & alternative treatments
 3. Harms and risk
 4. Cost
 5. Prevalence of treatment
 6. Clinical research study is reasonable

FINAL 1/10/2013



¹Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

HERC Coverage Guidance – Treatment of Attention Deficit Hyperactivity Disorder Disposition of Expert Comments

Expert	#	Comment	Disposition
Ajit Jetmalani	1	Practice based evidence is as important as evidence based practice in the world of Medicaid insured individuals where there is a much higher incidence of psychosocial stress / trauma / comorbid psychiatric disorders and genetic risks and developmental challenges. As you know, these comorbid interactive conditions are rarely considered in the evidence base practice populations.	The EbGS agrees that the population considered in the evidence report is narrow and likely excludes most patients with comorbidities
	2	So, in fact, if a child with multiple comorbid conditions came in with ADHD / disruptive behavior disorder over age six, a competent clinician would indeed institute non pharmacologic therapy <i>first</i> . After making certain that the child is in a safe home, they might implement trauma CBT, Collaborative Problem Solving (an AMH approved practice) training for the parent / foster family and then rule out a learning issue before ever getting to medication as an option. To make the recommendations more effective, could add some language such as: "primary ADHD without comorbid diagnoses" ..or .."where ADHD symptoms occur in the context of trauma or complex clinical presentations, ADHD may be secondary and medical treatment should await diagnostic clarification and or non medical strategies".	The EbGS agrees that this guidance is limited to patients without comorbidity; clarification added to the box
	3	In the case of a child who is living in a home with an abusive parent (noted by the psychologist), obviously, safety and then trauma needs to be addressed if ADHD symptoms will every be correctly treated.	The EbS agrees, this would represent a comorbid condition which should be treated first.
Joel Nigg, Ph.D., Professor Director, Division of Psychology	4	For children under 6, parent training as first line, pharmacotherapy as second line, is correct. I would however allow a stronger support for teacher/day care consultation in cases where parents are ineffective regardless of SES	Thank you for your comment. Teacher/daycare consultation is beyond the scope of this guidance.
Department of Psychiatry	5	Recs for older children are also sensible but again, allow for school consultation as it is proven effective and I would not limit this based on SES, because there is so much variation in school and parent skill even within SES	See comment #4.
Oregon Health	6	Regarding the psychologists concern about exceptional cases where there is a lot of abuse, domestic violence, or PTSD in younger children, I think both sides have a valid point. It is true that the evidence base for effectiveness of individual therapy (CBT, or other)	See comment #2

HERC Coverage Guidance – Treatment of Attention Deficit Hyperactivity Disorder Disposition of Expert Comments

Expert	#	Comment	Disposition
OHSU & Science University		with children with ADHD is negative, but for children with trauma the evidence is really sparse and one can find clinical experience that it provides meaningful support to ease suffering for children. It might make sense to allow this in some cases with adequate justification/documentation.	
	7	The 4.4% prevalence of ADHD in adults from Kessler et al NCS study has been challenged. Other studies (Simon et al) suggest more like 2.5%	Thank you for this information. As this was extracted directly from the AHRQ report and does not directly impact guidance rationale, the EbGS has elected not to change it.
	8	ADHD was first described by Benjamin Rush in 1812 in the USA; and was described by physicians in Europe in the 1800's. I would not cling to the 1902 citation for first description	See comment #7.
	9	What is the role of assessment? This is not clear in the guideline and perhaps is beyond their scope.	This document is not intended to serve as a practice guideline. Assessment is beyond the scope of the document.
	10	In the MTA study, the medication treatment group outperformed the community treatment group and had a higher success rate, by a lot, in the first year. This was attributed to the opportunity for 2 weeks dose and med titration. This would suggest that insurance should support dose titration and obtaining of blind ratings by teachers/parents and/or use of placebos during run-in, to ensure optimal dosage	See comment #9.
	11	Psychological and neuropsychological assessment can be a valuable guide to educational planning, e.g., when children have significant problems in executive functioning, memory, learning, or attention or have a non-verbal learning pattern that can be used by special education staff. Should insurance allow for targeted neuropsychological evaluation in cases of ADHD that are marked by significant learning failure despite treatment?	See comment #9.

HERC Coverage Guidance – Treatment of Attention Deficit Hyperactivity Disorder

Disposition of Public Comments

General Comments

Stakeholder	#	Comment	Disposition
<i>Pediatrician</i> Salem, OR	1	This on the whole appears to be well thought out incorporation of the latest information on ADHD treatment for children. Three areas of clarification I would request: 1. Clarity around the age. Guideline is written to say older than 6. I interpret this as 7 years or older. The latest ADHD guideline separates recommendations prior to 6th birthday or after 6th birthday. Simple clarification could be "6 years and older" when age is referenced.	Guidance changed to reflect this wording.
	2	2. You quote evidence on better tolerability of methylphenidate and mixed amphetamine salts. This is well known and clinicians in my office often do start with methylphenidate products. My concern is mixed amphetamine salts are not listed in concluding paragraph as recommend treatment for children. They are FDA approved and equally effective. Many patients tolerate them better so the availability of the option needs to be clear. My concern is medical directors would interpret the concluding paragraph to imply that only methylphenidate was recommended pharmacologic treatment.	The summary paragraph only lists MPH and atomoxetine because those are the only two agents that the evidence source determined to have a low strength of evidence for long-term (>12 mo) effectiveness. The evidence source states "many researchers and clinicians assume all psychostimulants are effective and safe for extended periods of time. The documentation for this assertion is not yet robust." The only medication for which there is evidence of poorer tolerability was guanfacine. There were no comparative long-term studies of MAS to another stimulant included in the review.
	3	3. I agree that behavior support should be first line for children prior to 6 years old. Unfortunately this service is lacking in most communities and even when available is difficult to access. A statement stating something to the effect of "if behavior therapy is unavailable for a patient or is ineffective in reaching patient and family goals, then medications should be considered." would be helpful.	According to comment #6 and #7, OPEC provides parenting education throughout much of the state.
<i>Health Plan Medical Director</i> Coos Bay, OR	4	Thanks for an excellent review. When you reviewed the evidence, did you find any evidence for doses of stimulants above the package insert recommended doses? We frequently see requests for escalating doses, yet some of my resources say there is little evidence for improvement over, for example, 30mg of Adderall XR. If there is good evidence to support escalating doses (or not escalation doses), that would be useful new clinical information for us to take to our physicians. Thanks again for your work.	For the most part, dosages were not specified in the evidence source. When they were, the highest noted dose for MPH was 54mg, for MAS was 30 mg, for atomoxetine was 2.0 mg/kg/day, for guanfacine was 4 mg/day. Table of included medications and FDA approved doses added to the guidance.

HERC Coverage Guidance – Treatment of Attention Deficit Hyperactivity Disorder Disposition of Public Comments

Stakeholder	#	Comment	Disposition
Physician Bend, Oregon	5	The HERC coverage guidelines are fairly complete regarding stimulant treatment of ADHD. The guidelines do not discuss comorbid conditions and the complexity they add to treatment. Additionally, the need for school communication to obtain information on diagnosis and assess treatment is not mentioned. Frequency of follow up is also important, especially regarding monitoring and record keeping to modify treatment as needed. We could tie up treatment recommendations including parent training and comorbidity and expand the resources available to an interested clinician by including the American Academy of Pediatrics 2011 revised guidelines: http://pediatrics.aappublications.org/content/early/2011/10/14/peds.2011-2654.full.pdf and the 2007 American Academy of Child and Adolescent Psychiatry recommendations: http://www.aacap.org/galleries/PracticeParameters/JAACAP_ADHD_2007.pdf In their present form, the HERC ADHD treatment guidelines add too little to clinicians' knowledge to be helpful.	The guidance document is a derivative product that is based on the AHRQ systematic review of the evidence. It is not intended to serve as a practice guideline, but as a recommendation for coverage. Thank you for providing these references. They do not conflict with the coverage guidance statements.
Outreach Coordinator Corvallis, OR	6	It is heartening to see the potential of parenting education included in the coverage for families who have young children diagnosed with ADHD in the HERC draft coverage document. Research has shown that effective early parenting contributes to later development of cognitive and social skills, positive peer relationships, and prevention of delinquency, risky behaviors, and school failure. Research also indicates that differences in parenting practices account for up to 50 percent of the gaps in school readiness. Effective parenting education programs have been linked with decreased rates of child abuse and neglect, better physical, cognitive and emotional development in children, increased parental knowledge of child development and parenting skills, improved parent-child communication, reduced youth substance abuse, and more effective parental monitoring and discipline. Of the parenting education programs suggested in the HERC document, The Incredible Years is the most widely used in Oregon. The program would be easily accessible to parents throughout the state, including rural areas.	Thank you for your comment.
	7	There are many organizations and agencies throughout the state that offer parenting education. There is not an umbrella agency in Oregon with the responsibility of overseeing the broad implementation of parenting education in the state. Therefore, it is difficult to generalize about the quality of implementation by all organizations. Oregon State University has been working for several years to evaluate and provide technical assistance to grantees funded by private foundations to provide parenting education programs in their local communities. The newest initiative is the Oregon Parenting Education Collaborative (OPEC). OPEC is a partnership between four of Oregon's largest foundations (The Oregon Community Foundation, The Ford Family Foundation, the Meyer Memorial Trust and The Collins Foundation) and Oregon State University (OSU). In addition to funding, OPEC supports grantees through evaluation, technical assistance, and professional development led by OSU. This is a multi-year grant program to support the delivery of evidence-based parenting education programs, increase access for parents to quality programs and to	Thank you for providing this information.

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Stakeholder	#	Comment	Disposition
		provide leadership in coordinating existing programs within their regions. OPEC has created eleven parenting education “Hubs” that reach 19 of 36 Oregon counties. (The vision is that by 2020, the initiative would be statewide.) Grantees are held to a high degree of accountability in their delivery of evidence-based programs. All facilitators must be trained by a professional trainer representing the curricula and implemented in the recommended manner. In addition, all OPEC Hubs are extensively evaluated. Outcomes are available for individual parents, as well as for the system. For information about the OPEC initiative, visit http://www.oregoncf.org/receive/grants/grant-opportunities/ready-to-learn/parent-ed-collaborative . This webpage also has links to the OPEC First Year Report, A Snapshot of Parenting Education in Oregon, and What We Know about Parenting Education.	
	8	I believe that there is great potential for community-based organizations to meet the needs of parenting education as proposed by HERC. Many of them are prepared to fill the need immediately. If you would like more information about the evaluation we have been conducting or about OPEC, please let me know.	Thank you for your comment.
Lilly Indianapolis, IN	9	HERC has requested public comment on its draft coverage guidance on the treatment of ADHD. On page 6 of the guidance, overall summary states: ¹ “There is evidence to support the long-term effectiveness of both methylphenidate and atomoxetine for improving ADHD symptoms, as well as methylphenidate combined with psychosocial interventions, in children age six and over.” ¹ However, the guidance does not recommend atomoxetine. ¹ Lilly is submitting the following evidence as supplementary support for the recommendation of atomoxetine as another first-line treatment option for ADHD.	The guidance recommends “psychostimulant medication.” While it is understood that atomoxetine is not a true stimulant, some resources refer to it as a psychostimulant. Wording changed to “pharmacotherapy,” limited to medications with FDA approval to treat ADHD.
	10	“For a decade, Oregon has led the nation in methamphetamine-treatment admissions per 100,000 people; treatment admissions for methamphetamine are second only to those for alcohol...Although many people believe those addicted to methamphetamine do not recover, their rate of recovery is about the same as that for people addicted to cocaine, heroin and other stimulants.” ² Atomoxetine has not shown a pattern of response that suggests stimulant or euphoric properties. ^{3-4, 13} Furthermore, clinical study data in over 2000 children, adolescents, and adults with ADHD and over 1200 adults with depression showed only isolated incidents of drug diversion or inappropriate self-administration associated with atomoxetine. ¹³	Thank you for this information.
	11	The review did not take into account evidence-based guidelines, which HERC considers as high-medium quality evidence. ⁵ Atomoxetine use has been discussed in various guidelines. AACAP (2007) ⁶ treatment guidelines suggest “an initial treatment plan that includes atomoxetine, amphetamine or methylphenidate preparations.” ⁶ The guidelines state atomoxetine “may be considered as the first medication for ADHD in persons with an active substance abuse problem, comorbid anxiety, or tics.” ⁶ Atomoxetine is preferred in patients who experience severe side effects to stimulants, such as mood lability or tics. ⁶ CADDRA (2011) ⁷ lists atomoxetine as a first-line agent for ADHD. ⁷ The guidelines state that atomoxetine may be particularly useful to ADHD patients with tic spectrum disorders or comorbid anxiety, and resistance and/or side effects	Thank you for providing these references. AACAP guideline states, “Direct comparisons of the efficacy of atomoxetine with that of MPH and amphetamine have shown a greater treatment effect of the stimulants.” CADDRA is the Canadian ADHD Resource Alliance. EbGS does not base their

HERC Coverage Guidance – Treatment of Attention Deficit Hyperactivity Disorder Disposition of Public Comments

Stakeholder	#	Comment	Disposition
		to stimulant medications, including problems with worsening of sleep. ⁷ NICE (2008) ⁸ recommends that healthcare professionals should consider methylphenidate or atomoxetine when tics, Tourette's syndrome, anxiety disorder, stimulant misuse, or risk of stimulant diversion are present. ⁸ Among FDA-approved non-stimulant agents, AAP (2011) ⁹ ranks the level of evidence for the treatment of elementary school-aged children (6-11 years of age) in the order of atomoxetine, followed by extended-release guanfacine, and extended-release clonidine. ⁹	decisions on the decisions of other guideline groups. Preferred treatment algorithms may be decided by other entities.
	12	Furthermore, the review only considered evidence up to May 2010. Since May 2010, additional evidence has been published supporting comparable efficacy for atomoxetine vs. methylphenidate in children/adolescents with ADHD (Please see attached publications for details). ¹⁰⁻¹²	Preferred treatment algorithms may be decided by other entities. Hanwella: meta-analysis of 9 RCTs of atomoxetine vs. MPH, longest trial was 12 weeks. Found no difference in efficacy, response rate or acceptability (measured by all-cause discontinuation). On subgroup analysis, MPH OROS was more efficacious than atomoxetine, although immediate release MPH was not. Hazell: meta-analysis of 7 RCTs of atomoxetine vs. MPH, longest trial was 10 weeks. Found similar response rates. van Wyk: meta-analysis 7 RCTs of atomoxetine vs. MPH, longest trial was 10 weeks. Found similar response to treatment, overall, and in patients with ODD. Response based on subtype (hyperactive, inattentive) also showed no difference.
	13	In closing, atomoxetine's value summary is: - Atomoxetine offers continuous efficacy and has been proven effective in both hyperactive/impulsive and inattentive symptoms of ADHD. - Atomoxetine provides long-term control of ADHD symptoms with proven maintenance treatment in children/adolescents. - Atomoxetine is not a scheduled substance.¹³ - Atomoxetine does not worsen anxiety or tics in patients with ADHD and co-existing Tourette's disorder or anxiety disorders.¹³⁻¹⁵	EbGS does not dispute the efficacy and safety of atomoxetine and other FDA approved medications for ADHD.

HERC Coverage Guidance – Treatment of Attention Deficit Hyperactivity Disorder Disposition of Public Comments

Stakeholder	#	Comment	Disposition
		Proven safety and tolerability profile in children, adolescents, and adults.	
	14	<u>Safety and Tolerability</u> Please see full prescribing information for complete safety information. - Strattera (atomoxetine) contains a black box warning about an increased risk for suicidal ideation in children and adolescents with ADHD; therefore, anyone considering the use of Strattera in a child or adolescent must balance this risk with the clinical need. All pediatric patients who are started on therapy should be monitored closely for suicidality (suicidal thinking and behavior), clinical worsening, or unusual changes in behavior, especially during the initial few months of drug therapy or at times of dose changes, either increases or decreases.¹³ Families and caregivers should be advised of the need for close observation and communication with the prescriber.¹³ Strattera is approved for ADHD in pediatric and adult patients.¹³ Strattera is not approved for major depressive disorder.¹³ Pooled analyses of short-term (6 to 18 weeks) placebo-controlled trials of Strattera in children and adolescents (a total of 12 trials involving over 2200 patients, including 11 trials in ADHD and 1 trial in enuresis) have revealed a greater risk of suicidal ideation early during treatment in those receiving Strattera compared to placebo.¹³ The average risk of suicidal ideation in patients receiving Strattera was 0.4% (5/1357 patients), compared to none in placebo-treated patients (851 patients).¹³ No suicides occurred in these trials. A similar analysis in adult patients treated with Strattera for either ADHD or major depressive disorder (MDD) did not reveal an increased risk of suicidal ideation or behavior associated with the use of Strattera.¹³ - Strattera is contraindicated in patients known to be hypersensitive to Strattera or other constituents of the product, and in patients with narrow angle glaucoma, pheochromocytoma or a history of pheochromocytoma, or severe cardiovascular disorders.¹³ - Strattera should not be taken with a Monoamine Oxidase Inhibitor (MAOI) or within 14 days after discontinuing an MAOI or other drugs that affect brain monoamine concentrations.¹³ - Strattera can cause severe liver injury and should be discontinued and not restarted in patients with jaundice or laboratory evidence of liver injury.¹³ - Strattera should not be used in patients with severe cardiovascular disorders whose condition would be expected to deteriorate if they experience increases in blood pressure or heart rate that could be clinically important (e.g., 15 to 20 mm Hg in blood pressure or 20 beats per minute in heart rate).¹³ Strattera should be used with caution in patients whose underlying medical conditions could be worsened by increases in blood pressure or heart rate such as certain patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease.¹³ Pulse and blood pressure should be measured at baseline, following Strattera dose increases, and periodically while on therapy to detect possible clinically important increases.¹³	Thank you for this information.

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Disposition of Public Comments

Stakeholder	#	Comment	Disposition
		• Strattera at usual doses can cause treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania.¹³ Discontinuation of treatment with Strattera should be considered if such symptoms occur.¹³ • Other potentially serious side effects include slowing of growth, priapism, and difficulty urinating.¹³	

DRAFT

Section 7.0

New Discussion Items

Extracorporeal Photopheresis

Question: Should extracorporeal photopheresis (CPT 36522) be added for treatment of certain conditions on the Prioritized List?

Question source: DMAP; Shernan Holtan, MD, OHSU Center for Hematologic Malignancies

Issue: Currently, extracorporeal photopheresis (CPT 36522) is only included on line 622 SECONDARY AND ILL-DEFINED MALIGNANT NEOPLASMS. Dr. Holtan is requesting review of its use for graft vs. host disease and cutaneous T cell lymphoma. This procedure is has also been used for treatment of a series of other, mostly autoimmune conditions.

Extracorporeal photopheresis is a form of apheresis and photodynamic therapy in which blood is treated with photoactivable drugs which are then activated with ultraviolet light. This treatment has immunomodulatory and anti-cancer effects through a mechanism that is not well understood.

Cutaneous T cell lymphoma

Cutaneous T cell lymphoma is a neoplasm, with subtypes identified as mycosis fungoides and the Sézary syndrome (MF/SS). These kinds of neoplasms initially present as skin involvement. The prognosis of patients with MF/SS is based on the extent of disease at presentation (stage). Patients with stage IA disease have a median survival of 20 or more years. The majority of deaths for this group are not caused by, nor are they related to, MF. In contrast, more than 50% of patients with stage III through stage IV disease die of MF, with a median survival of less than 5 years. Typically, the natural history of MF is indolent. Symptoms of the disease may present for long periods, an average of 2 to 10 years, as waxing and waning cutaneous eruptions prior to biopsy confirmation. MF/SS is treatable with available topical and/or systemic therapies. Curative modalities, however, have thus far proven elusive, with the possible exception of patients with minimal disease confined to the skin.

Current Prioritized List information:

Mycosis fungoides (ICD-9 202.1x) and Sezary syndrome (ICD-9 202.2x) are located on lines 170 and 221 NON-HODGKIN'S LYMPHOMAS. Line 170 is for bone marrow transplant and line 221 is for other medical therapies.

GVHD

Graft-versus-host disease (GVHD) is a common complication following an allogeneic tissue transplant. It is commonly associated with stem cell or bone marrow transplant but the term also applies to other forms of tissue graft. Immune cells (white blood cells) in the tissue (the graft) recognize the recipient (the host) as "foreign". The transplanted immune cells then attack the host's body cells.

Current Prioritized List information:

Acute (ICD-9 279.51), chronic (ICD-9 279.52) and acute-on-chronic graft versus host disease (ICD-9 279.53) are located on lines 308 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT and 338 DISORDERS INVOLVING THE IMMUNE SYSTEM.

Expert input

Extracorporeal Photopheresis

Kevin Olson, MD

The quality of evidence is not high but balancing that reality is the fact that the diseases where this is useful are rare and therefore not amenable to large randomized trials.

The technology is such that overuse or abuse is unlikely. I have seen this used rarely in the last several years.

Also balancing the discussion is the fact that GVH and CTCL are both diseases that have significant morbidity and standard, covered drug therapies are likely to be even more expensive than photopheresis

Sherman Holtan, MD

ECP is an important therapy for GVHD that is dependent on steroids, or refractory to steroids, as no standard therapy exists for these patients. ECP is particularly useful in that it relatively spares one's ability to fight infections compared to other systemic immunosuppressants.

Extracorporeal Photopheresis

Evidence

Cutaneous T cell lymphoma

1) NICE

- a. As of 2003, NICE considers photopheresis to be standard clinical procedure for treatment of cutaneous T cell lymphoma

2) Scarisbrick et al 2007

- a. Systematic review and consensus statement for use of extracorporeal photopheresis in the UK
- b. 30 studies (N=689 patients)
- c. Mean response rate of 63% (range 43–100%); response rates were higher in those with erythrodermic CTCL.
- d. The differences in response rates between centres may relate to different patient selection for treatment with ECP such as the presence of a peripheral T-cell clone, stage of disease, prior treatment, ECP protocol, duration of ECP and definition of response
- a. Extracorporeal photopheresis (ECP) should be considered for the treatment of patients with cutaneous T-cell lymphoma (CTCL) who fulfill both major criteria and one of the minor criteria as listed below
 - i. Major criteria
 - 1. Erythroderma
 - 2. Stage III or IVA CTCL (histology consistent with CTCL)
 - ii. Minor criteria
 - 1. Circulating clonal disease [circulating T-cell clone by polymerase chain reaction (PCR) or Southern blot analysis (SBA)]
 - 2. Evidence of circulating Sezary cells (> 10% of circulating lymphocytes)
 - 3. CD4/CD8 ratio > 10

3) Ontario Health Technology Assessment 2006

- a. Overall, there is low-quality evidence that ECP improves response rates and survival in patients with refractory erythrodermic CTCL
- b. For refractory erythrodermic CTCL, the overall GRADE and strength of the recommendation is “weak” – the quality of the evidence is “low” (uncertainties due to methodological limitations in the study design in terms of study quality and directness),
- c. the cost-effectiveness of ECP is unknown and difficult to estimate considering that there are no high quality studies of effectiveness.

4) McKenna 2006

- a. Evidence based review for photopheresis for UK
- b. There is fair evidence for the use of ECP in erythrodermic CTCL, but randomized controlled studies are needed.
- c. There is good evidence to support the rejection of the use of ECP for the treatment of nonerythrodermic MF. [CTCL, nonerythrodermic (stage IA–IIB): Strength of Recommendation E, Quality of Evidence I; CTCL, erythrodermic (stage III/IVA/B1/0): Strength of Recommendation B, Quality of Evidence II-i.]

Graft vs host disease

1) Scarisbrick et al 2007

- a. Systematic review and consensus statement for use of extracorporeal photopheresis in the UK

Extracorporeal Photopheresis

- b. 23 studies (N=521 patients)
- c. The response rate in skin GVHD was reported in 18 studies with a mean response of 68% (range 29–100%) and complete responses being achieved in some patients; response rates in the liver were reported in 10 studies with a mean response of 63% and response rates in the mucosa were reported in nine studies with a mean response of 63%.
- d. Extracorporeal photopheresis (ECP) should be considered for patients with chronic extensive graft-versus-host disease (GVHD) as defined by the standard criteria revised by the Seattle group in 2002
- e. Inclusion criteria
 - i. Patients must require second-line/third-line salvage therapy because of either steroid-refractory or steroid-dependent disease. Steroid refractory is defined as minimal or no response to prednisolone 1 mg/kg¹ or equivalent after a minimum of 4 weeks of treatment; steroid dependent is defined as the inability to reduce steroids to prednisolone < 10 mg or equivalent daily without flare of GVHD
 - ii. Alternatively, patients must be unable to tolerate standard first-line corticosteroid therapy
 - iii. Patients must have chronic GVHD (cGVHD) primarily affecting at least one of the following organs: skin; mucosal membranes (mouth and/or eye disease); liver
 - iv. GVHD affecting other organs does not preclude ECP treatment and should be monitored for response. However, there is inadequate evidence to recommend ECP in the absence of the above manifestations.
 - v. Patients should have cGVHD confirmed with compatible histology from an affected organ biopsy wherever possible.

2) Ontario Health Technology Assessment 2006

- a. Overall, there is low-quality evidence that ECP improves response rates and survival in patients with refractory cGVHD
- b. For refractory cGVHD, the overall GRADE and strength of the recommendation is “weak” – the quality of the evidence is “low” (uncertainties due to methodological limitations in the study design in terms of study quality and directness)
- c. The cost-effectiveness of ECP is unknown and difficult to estimate considering that there are no high quality studies of effectiveness.

3) McKenna 2006

- a. Evidence based review for photopheresis for UK
- b. There is fair evidence for the use of ECP in steroid-refractory GVHD, but randomized controlled studies are needed.
- c. There is fair evidence to support the use of ECP in cGVHD with cutaneous or mucosal involvement, but the evidence in hepatic disease is poor. There is fair evidence to support the rejection of the use of ECP for gastrointestinal or pulmonary cGVHD. (cGVHD cutaneous/mucous membranes: Strength of Recommendation B, Quality of Evidence II-ii; cGVHD hepatic: Strength of Recommendation C, Quality of Evidence II-iii; cGVHD gastrointestinal/pulmonary: Strength of Recommendation D, Quality of Evidence II-ii.)
- d. There is poor evidence to support the use of ECP for cutaneous or hepatic aGVHD. (aGVHD cutaneous/hepatic: Strength of Recommendation C, Quality of Evidence II-iii.)

Extracorporeal Photopheresis

Other indications

1) Cardiac transplant rejection

a. McKenna 2006

- i. Evidence based review for photopheresis for UK
- ii. There is good evidence supporting the use of ECP in preventing cardiac rejection following transplantation.
- iii. there is good evidence to support the use of ECP for the treatment of acute rejection, recurrent acute rejection, prophylaxis of rejection and chronic cardiac rejection. (Strength of Recommendation A, Quality of Evidence I.)

Guidelines

1) American Society of Apheresis (ASFA) 2013

- a. Cardiac transplant rejection—second line therapy (Strong recommendation, moderate evidence)
- b. Erythrodermic cutaneous T cell lymphoma—first line therapy (Strong recommendation, moderate evidence)
- c. Graft vs. host disease (chronic, skin)—second line therapy (Strong recommendation, moderate evidence)
- d. Graft vs. host disease (acute, skin)—second line therapy (Strong recommendation, weak evidence)
- e. Graft vs. host disease (acute/chronic, non-skin)—unclear role

Other policies

1) CMS 2006

- a. Coverage of photopheresis for
 - i. Palliative treatment of skin manifestations of CTCL that has not responded to other therapy.
 - ii. Patients with acute cardiac allograft rejection whose disease is refractory to standard immunosuppressive drug treatment; and
 - iii. Patients with chronic graft versus host disease whose disease is refractory to standard immunosuppressive drug treatment.

2) Premara BCBS 2013

- a. Extracorporeal photopheresis may be considered **medically necessary** to treat cardiac allograft rejection, including acute rejection, that is either recurrent or that is refractory to standard immunosuppressive drug treatment. Extracorporeal photopheresis is considered **investigational** in all other situations related to treatment or prevention of rejection in solid-organ transplantation
- b. Extracorporeal photopheresis may be considered **medically necessary** as a technique to treat chronic graft-versus-host disease that is refractory to medical therapy. Extracorporeal photopheresis is considered **investigational** as a technique to treat acute graft-versus-host disease or chronic graft-versus-host disease that is either previously untreated or is responding to established therapies.
 - i. The evidence for the use of ECP for the treatment of GVHD relates to both chronic and acute GVHD in pediatric and adult populations. The published literature is lacking randomized trials. The evidence consists of

Extracorporeal Photopheresis

retrospective reviews and non-randomized comparisons. These data consistently show improvement in GVHD that is unresponsive to standard therapy and are consistent with the conclusions from the 2001 TEC Assessment. Additionally, there are a lack of other treatment options for these patients, with the added benefit of minimal side effects from ECP, as well as the possibility of reduction and often a cessation of treatment with corticosteroids and other immunosuppressive agents if there is a response to ECP

- c. Extracorporeal photopheresis may be considered **medically necessary** as a technique to treat late-stage (III/IV) cutaneous T-cell lymphoma. Extracorporeal photopheresis may be considered **medically necessary** as a technique to treat early stage (I/II) cutaneous T-cell lymphoma that is progressive and refractory to established nonsystemic therapies. Extracorporeal photopheresis is considered **investigational** as a technique to treat early stage (I/II) cutaneous T-cell lymphoma that is either previously untreated or is responding to established nonsystemic therapies.
 - i. The evidence from small case series has shown a response to ECP in patients with advanced stage CTCL, as well as prolongation of survival in a proportion of patients. Therefore, in this policy, ECP may be considered medically necessary as a technique for the treatment of patients with stages III/IV CTCL. Given the unfavorable prognosis for patients with early-stage CTCL that progresses while receiving nonsystemic therapies, the relative lack of adverse events with ECP compared to other systemic treatments, and the good response rates often associated with ECP, ECP may be considered medically necessary as a technique for the treatment of patients with refractory or progressive early-stage CTCL. By contrast, when early-stage CTCL does respond to less-invasive, topical therapies, patients whose disease remains quiescent under such treatments usually experience a near-normal life expectancy

3) Aetna 2013

- a. Aetna considers extracorporeal photochemotherapy (ECP, photopheresis) medically necessary for erythrodermic variants of cutaneous T cell lymphoma (e.g., mycosis fungoides, Sézary syndrome).
- b. Aetna considers ECP medically necessary in the treatment of acute cardiac allograft rejection that is refractory to standard immunosuppressive drug treatment (high-dose steroids plus 2 or more of the following, unless contraindicated: azathioprine, cyclosporine, methotrexate, and/or polyclonal and monoclonal antilymphocyte agents (e.g., anti-lymphocyte globulin (ALG) and anti-thymocyte globulin (ATG)).
- c. Aetna considers extracorporeal photochemotherapy medically necessary in the treatment of rejection (bronchiolitis obliterans) of lung transplants that are refractory to immunosuppressive drug treatment (high-dose steroids plus 2 or more of the following, unless contraindicated: azathioprine, cyclosporine, tacrolimus, and/or polyclonal and monoclonal antilymphocyte agents (e.g., ALG and ATG)).
- d. Aetna considers ECP medically necessary for the treatment of graft-versus-host disease of an allogeneic bone marrow or stem cell transplant when the disease is refractory to standard immunosuppressive drug treatment.

Summary:

Extracorporeal Photopheresis

There is moderate evidence for the use of extracorporeal photopheresis for treatment of erythrodermic cutaneous T-cell lymphoma and chronic graft-versus-host disease for select patients, although the evidence base is not robust.

Extracorporeal Photopheresis

HERC staff recommendations:

- 1) Add extracorporeal photopheresis (CPT 36522) to line 221 NON-HODGKIN'S LYMPHOMAS for treatment of cutaneous T cell lymphoma and to line 338 DISORDERS INVOLVING THE IMMUNE SYSTEM. for treatment of chronic graft-versus-host disease
- 2) Remove CPT 36522 from line 622 SECONDARY AND ILL-DEFINED MALIGNANT NEOPLASMS
- 3) Adopt the following new guideline:

GUIDELINE NOTE XXX EXTRACORPOREAL PHOTOPHERESIS

Lines 221, 338

Extracorporeal photopheresis (CPT 36522) is included on line 221 for treatment of chronic T-cell lymphoma (ICD-9 202.1x, 202.2x; ICD-10 C84.0, C84.1) which is:

- 1) stage III or IVA
- 2) erythroderma
- 3) not responsive to other therapy

Extracorporeal photopheresis (CPT 36522) is included on line 338 for treatment of chronic graft-versus-host disease (ICD-9 279.52; ICD-10 T86.0) which

- 1) is steroid refractory, steroid dependent or the patient is unable to tolerate corticosteroid therapy
- 2) primarily affects skin or mucosal membranes (mouth and/or eye disease)

U.K. consensus statement on the use of extracorporeal photopheresis for treatment of cutaneous T-cell lymphoma and chronic graft-versus-host disease

J.J. Scarisbrick, P. Taylor,* U. Holtick,† Y. Makar,‡ K. Douglas,§ G. Berlin,¶ E. Juvonen** and S. Marshall† on behalf of the Photopheresis Expert Group

St John's Institute of Dermatology, St Thomas' Hospital, London SE1 7EH, U.K.

*Department of Haematology, Rotherham District General Hospital, Rotherham, U.K.

†Department of Haematology, Royal Victoria Infirmary, Newcastle upon Tyne, U.K.

‡Manchester Blood Centre, National Blood Service, Manchester, U.K.

§Glasgow Royal Infirmary, Glasgow, U.K.

¶Haematology Department, University Hospital of Linköping, Linköping, Sweden

**Haematology Department, Helsinki University, Helsinki, Finland

Summary

Correspondence

Julia Scarisbrick.

E-mail: juliascarisbrick@doctors.net.uk

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Conflicts of interest

None declared.

In addition to the authors, the Photopheresis Expert Group comprises Kristin Ryggen (Trondheim, Norway), Ian Gosling, Ruti Leci and Sukran Saglam (St John's Institute of Dermatology), Emma Das-Gupta, Rebecca Ellis and Lynne Watson (Nottingham City Hospital), Carol Shaw (National Blood Service, Manchester), Eileen Parry (Manchester Hope Hospital), Gordon Cook (Leeds St James' Hospital), Fiona Clark (University Hospitals Birmingham) and Curly Morris and Mary Drake (Belfast City Hospital).

Extracorporeal photopheresis (ECP) has been used for over 30 years in the treatment of erythrodermic cutaneous T-cell lymphoma (CTCL) and over 20 years for chronic graft-versus-host disease (cGVHD). The lack of prospective randomized trials has led to different centres having different patient selection criteria, treatment schedules, monitoring protocols and patient assessment criteria. ECP for CTCL and cGVHD is available only at six specialized centres across the U.K. In the recent Improving Outcomes Guidance the National Institute for Health and Clinical Excellence endorsed the use of ECP for CTCL and because of the complexity of treatment supported its use in specialized centres and also suggested the need for expansion of this service. In 2005 consultants and senior nurses from all U.K. sites and from Scandinavia formed a Photopheresis Expert Group. This group's first aim was to produce a consensus statement on the treatment of CTCL and cGVHD with ECP using evidence-based medicine and best medical practice, in order to standardize ECP eligibility, assessment and treatment strategies across the U.K.

Extracorporeal photopheresis (ECP) is a cell-based immunomodulatory therapy involving the separation of leucocyte-rich plasma followed by ex-vivo administration of a photosensitizer and ultraviolet (UV) A radiation before reinfusion. The approach was first published in 1987 by Edelson et al. who reported the use of photopheresis in the treatment of erythrodermic cutaneous T-cell lymphoma (CTCL) in a multicentre trial.¹ The UVAR system for ECP (Therakos, Exton, PA, U.S.A.) was granted approval by the U.S. Food and Drug Administra-

tion in 1988. Since this time data have been published on over 1000 patients with CTCL treated with ECP from centres worldwide. These findings have verified those of Edelson et al. and have cited response rates of 43–100% with complete responses of 0–62%.

ECP involves three stages: (i) leukapheresis; (ii) photoactivation with 8-methoxypsoralen (8-MOP)/UVA; and (iii) reinfusion of buffy coat. This procedure takes 3–4 h. During the collection phase whole blood enters a latham

Extracorporeal Photophoresis

An Evidence-Based Analysis

March 2006



Medical Advisory Secretariat
Ministry of Health and Long-Term Care

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Contact Information

The Medical Advisory Secretariat
Ministry of Health and Long-Term Care
20 Dundas Street West, 10th floor
Toronto, Ontario
CANADA
M5G 2N6
Email: MASinfo@moh.gov.on.ca
Telephone: 416-314-1092

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Executive Summary

Objective

To assess the effectiveness, safety and cost-effectiveness of extracorporeal photophoresis (ECP) for the treatment of refractory erythrodermic cutaneous T cell lymphoma (CTCL) and refractory chronic graft versus host disease (cGvHD).

Background

Cutaneous T Cell Lymphoma

Cutaneous T cell lymphoma (CTCL) is a general name for a group of skin affecting disorders caused by malignant white blood cells (T lymphocytes). Cutaneous T cell lymphoma is relatively uncommon and represents slightly more than 2% of all lymphomas in the United States. The most frequently diagnosed form of CTCL is mycosis fungoides (MF) and its leukemic variant Sezary syndrome (SS). The relative frequency and disease-specific 5-year survival of 1,905 primary cutaneous lymphomas classified according to the World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) classification (Appendix 1). Mycosis fungoides had a frequency of 44% and a disease specific 5-year survival of 88%. Sezary syndrome had a frequency of 3% and a disease specific 5-year survival of 24%.

Cutaneous T cell lymphoma has an annual incidence of approximately 0.4 per 100,000 and it mainly occurs in the 5th to 6th decade of life, with a male/female ratio of 2:1. Mycosis fungoides is an indolent lymphoma with patients often having several years of eczematous or dermatitic skin lesions before the diagnosis is finally established. Mycosis fungoides commonly presents as chronic eczematous patches or plaques and can remain stable for many years. Early in the disease biopsies are often difficult to interpret and the diagnosis may only become apparent by observing the patient over time.

The clinical course of MF is unpredictable. Most patients will live normal lives and experience skin symptoms without serious complications. Approximately 10% of MF patients will experience progressive disease involving lymph nodes, peripheral blood, bone marrow and visceral organs. A particular syndrome in these patients involves erythroderma (intense and usually widespread reddening of the skin from dilation of blood vessels, often preceding or associated with exfoliation), and circulating tumour cells. This is known as SS. It has been estimated that approximately 5-10% of CTCL patients have SS. Patients with SS have a median survival of approximately 30 months.

Chronic Graft Versus Host Disease

Allogeneic hematopoietic cell transplantation (HCT) is a treatment used for a variety of malignant and nonmalignant disease of the bone marrow and immune system. The procedure is often associated with serious immunological complications, particularly graft versus host disease (GvHD). A chronic form of GvHD (cGvHD) afflicts many allogeneic HCT recipients, which results in dysfunction of numerous organ systems or even a profound state of immunodeficiency. Chronic GVHD is the most frequent cause of poor long-term outcome and quality of life after allogeneic HCT. The syndrome typically develops several months after transplantation, when the patient may no longer be under the direct care of the

Evidence-based practice of photopheresis 1987–2001: a report of a workshop of the British Photodermatology Group and the U.K. Skin Lymphoma Group

K.E. McKenna, S. Whittaker,* L.E. Rhodes,† P. Taylor,‡ J. Lloyd,§ S. Ibbotson¶ and R. Russell-Jones*

Department of Dermatology, Belfast City Hospital, Belfast, U.K.

*Skin Tumour Unit, St John's Institute of Dermatology, Guy's and St Thomas' Hospital, London, U.K.

†Photobiology Unit, Dermatology Centre, University of Manchester, Hope Hospital, Salford, U.K.

‡Department of Haematology, Rotherham General Hospital, Rotherham, U.K.

§Regional Medical Physics Department, Newcastle-upon-Tyne, U.K.

¶Photobiology Unit, Department of Dermatology, Ninewells Hospital, Dundee, U.K.

Summary

Correspondence

K.E. McKenna.

E-mail: kevin.mckenna@bch.n-i.nhs.uk

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Key words:

cardiac transplant rejection, cutaneous T-cell lymphoma, extracorporeal photochemotherapy, graft-versus-host disease, Sézary syndrome

Conflicts of interest:

None declared.

Photopheresis or extracorporeal photochemotherapy (ECP) is a novel immunomodulatory therapy which involves separation of the patient's leucocyte-rich plasma, followed by *ex vivo* administration of a photosensitizer and ultraviolet A radiation, before reinfusion. ECP has been used successfully for the treatment of cutaneous T-cell lymphoma (CTCL: Sézary syndrome), graft-versus-host disease (GVHD) and cardiac transplant rejection. ECP has a dose-sparing effect on concurrent immunosuppressive therapy. The procedure induces apoptosis of the irradiated lymphocytes, but the exact mechanism by which ECP exerts its therapeutic effect in these different conditions is uncertain. The treatment has very few adverse effects and in particular is not associated with an increased incidence of opportunistic infections. The evidence for the efficacy of ECP has been appraised by a combined British Photodermatology Group and U.K. Skin Lymphoma Group workshop on the basis of evidence published up to the end of 2001 and on the consensus of best practice. There is fair evidence for the use of ECP in erythrodermic CTCL and steroid-refractory GVHD, but randomized controlled studies are needed. There is good evidence supporting the use of ECP in preventing cardiac rejection following transplantation. Randomized controlled trials have also shown a therapeutic benefit in type 1 diabetes mellitus, but the inconvenience associated with the procedure outweighed the clinical benefit. There is fair evidence not to use ECP for the treatment of systemic sclerosis and multiple sclerosis, and good evidence not to use ECP for other forms of CTCL.

Photopheresis or extracorporeal photochemotherapy (ECP) was first reported by Edelson *et al.* in 1987¹ and was approved by the U.S. Food and Drug Administration for the treatment of advanced cutaneous T-cell lymphoma (CTCL) in 1988. Since then its application has been reported in the treatment of a variety of other T-cell-mediated disorders including graft-versus-host disease (GVHD),² cardiac transplant rejection³ and type I diabetes mellitus.⁴ Other conditions where ECP has been used include other types of solid organ transplant rejection,⁵ scleroderma,⁶ multiple sclerosis (MS),⁷ bullous disorders,⁸ rheumatoid arthritis (RA),⁹ psoriasis,¹⁰ psoriatic arthritis,¹¹ atopic eczema,¹² systemic lupus erythematosus,¹³ discoid lupus erythematosus,¹⁴ lichen planus,¹⁵ AIDS-related complex,¹⁶ scleromyxoedema,¹⁷ scleredema,¹⁸ dermatomyositis,¹⁹ Lyme

arthritis,²⁰ chronic hepatitis C infection²¹ and chronic lymphocytic leukaemia.²² ECP is now used in 160 centres worldwide (Therakos, personal communication); however, the treatment is moderately expensive and time consuming, and approved indications are restricted. In addition, the mechanism(s) of action of ECP are still not fully understood and the optimum parameters for administration of this therapy and specific indications for its use require clarification. A joint British Photodermatology Group and U.K. Skin Lymphoma Group workshop was held in December 2001 to address these issues. The use of ECP for a variety of indications was appraised using criteria previously applied in guideline reports on the basis of evidence published in the English language^{23,24} (Appendix 1 and 2).

Guidelines on the Use of Therapeutic Apheresis in Clinical Practice—Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Sixth Special Issue

Joseph Schwartz,¹ Jeffrey L. Winters,² Anand Padmanabhan,³ Rasheed A. Balogun,⁴ Meghan Delaney,⁵ Michael L. Linenberger,⁶ Zbigniew M. Szczepiorkowski,⁷ Mark E. Williams,⁸ Yanyun Wu,⁹ and Beth H. Shaz^{10,11*}

¹Department of Pathology and Cell Biology, Columbia University Medical Center, New York, New York

²Division of Transfusion Medicine, Mayo Clinic, Rochester, Minnesota

³BloodCenter of Wisconsin, Milwaukee, Wisconsin

⁴Division of Nephrology, University of Virginia, Charlottesville, Virginia

⁵Puget Sound Blood Center, Seattle, Washington

⁶Department of Medicine, Seattle Cancer Care Alliance, Seattle, Washington

⁷Department of Pathology and Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire

⁸Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts

⁹Department of Laboratory Medicine, Yale University School of Medicine, New Haven, Connecticut

¹⁰New York Blood Center, New York, New York

¹¹Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, Georgia

The American Society for Apheresis (ASFA) JCA Special Issue Writing Committee is charged with reviewing, updating and categorizing indications for therapeutic apheresis. Beginning with the 2007 ASFA Special Issue (Fourth Edition), the committee has incorporated systematic review and evidence-based approach in the grading and categorization of indications. This Sixth Edition of the ASFA Special Issue has further improved the process of using evidence-based medicine in the recommendations by consistently applying the category and GRADE system definitions, but eliminating the “level of evidence” criteria (from the University HealthCare Consortium) utilized in prior editions given redundancy between GRADE and University HealthCare Consortium systems. The general layout and concept of a fact sheet that was utilized in the Fourth and Fifth Editions, has been largely maintained in this edition. Each fact sheet succinctly summarizes the evidence for the use of therapeutic apheresis in a specific disease entity. This article consists of 78 fact sheets (increased from 2010) for therapeutic indications in ASFA categories I through IV, with many diseases categorized having multiple clinical presentations/situations which are individually graded and categorized. *J. Clin. Apheresis* 28:145–284, 2013. © 2013 Wiley Periodicals, Inc.

Key words: apheresis, plasma exchange, immunoadsorption, leukocytapheresis, photopheresis, categories, indications, evidence based, red blood cell exchange, LDL apheresis, rheopheresis

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*Correspondence to: Beth H. Shaz, MD; New York Blood Center, New York, NY 10065. E-mail: bshaz@nybloodcenter.org

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National Coverage Determination (NCD) for Extracorporeal Photopheresis (110.4)

Select the 'Print Record', 'Add to Basket' or 'Email Record' buttons to print the record, to add it to your basket or to email the record.

Print Record

Email Record

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Tracking Information

Publication Number	Manual Section Number	Manual Section Title
100-3	110.4	Extracorporeal Photopheresis
Version Number	Effective Date of this Version	Ending Effective Date of this Version
2	12/19/2006	4/30/2012

Implementation Date

4/2/2007

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Benefit Category

Physicians' Services

Note: This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

Item/Service Description

Extracorporeal photopheresis is a medical procedure in which a patient's white blood cells are exposed first to a drug called 8-methoxypsoralen (8-MOP) and then to ultraviolet A (UVA) light. The procedure starts with the removal of the patient's blood, which is centrifuged to isolate the white blood cells. The drug is typically administered directly to the white blood cells after they have been removed from the patient (referred to as ex vivo administration) but the drug can alternatively be administered directly to the patient before the white blood cells are withdrawn. After UVA light exposure, the treated white blood cells are then re-infused into the patient.

Indications and Limitations of Coverage

B. Nationally Covered Indications

The CMS has determined that extracorporeal photopheresis is reasonable and necessary under §1862(a)(1)(A) of the Social Security Act under the following circumstances:

1. Effective April 8, 1988, Medicare provides coverage for:
 - Palliative treatment of skin manifestations of CTCL that has not responded to other therapy.
2. Effective December 19, 2006, Medicare also provides coverage for:

- Patients with acute cardiac allograft rejection whose disease is refractory to standard immunosuppressive drug treatment; and
- Patients with chronic graft versus host disease whose disease is refractory to standard immunosuppressive drug treatment.

C. Nationally Noncovered Indications

All other indications for extracorporeal photopheresis remain noncovered.

D. Other

Claims processing instructions can be found in chapter 32, section 190 of the Medicare Claims Processing Manual.

(This NCD last reviewed December 2006.)

Claims Processing Instructions

- [TN 1206 \(Medicare Claims Processing\)](#)
- [TN 2473 \(Medicare Claims Processing\)](#)
- [TN 2494 \(Medicare Claims Processing\)](#)
- [TN 2506 \(Medicare Claims Processing\)](#)
- [TN 2543 \(Medicare Claims Processing\)](#)
- [TN 2551 \(Medicare Claims Processing\)](#)

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Transmittal Number

66

Revision History

04/1988 - Provided coverage when used in the palliative treatment of skin manifestations of cutaneous T-cell lymphoma that has not responded to other therapy. Effective date 04/08/1988. (TN 24)

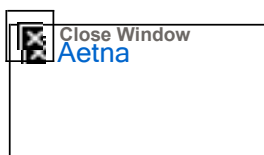
Extracorporeal photopheresis is now covered for patients with acute cardiac allograft rejection or chronic graft versus host disease whose disease is refractory to standard immunosuppressive drug treatment. Effective date 12/19/2006 Implementation date 04/02/2007. (TN 66)

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National Coverage Analyses (NCAs)

This NCD has been or is currently being reviewed under the National Coverage Determination process. The following are existing associations with NCAs, from the National Coverage Analyses database.

- [First reconsideration for Extracorporeal Photopheresis \(CAG-00324R\) opens in new window](#)
- [Second reconsideration for Extracorporeal Photopheresis \(ECP\) \(CAG-00324R2\) opens in new window](#)



Clinical Policy Bulletin:
 Extracorporeal Photochemotherapy (Photopheresis)
Number: 0241

Policy

1. Aetna considers extracorporeal photochemotherapy (ECP, photopheresis) medically necessary for erythrodermic variants of cutaneous T cell lymphoma (e.g., mycosis fungoides, Sézary syndrome).
2. Aetna considers ECP medically necessary in the treatment of acute cardiac allograft rejection that is refractory to standard immunosuppressive drug treatment (high-dose steroids plus 2 or more of the following, unless contraindicated: azathioprine, cyclosporine, methotrexate, and/or polyclonal and monoclonal antilymphocyte agents (e.g., anti-lymphocyte globulin (ALG) and anti-thymocyte globulin (ATG)).
3. Aetna considers extracorporeal photochemotherapy medically necessary in the treatment of rejection (bronchiolitis obliterans) of lung transplants that are refractory to immunosuppressive drug treatment (high-dose steroids plus 2 or more of the following, unless contraindicated: azathioprine, cyclosporine, tacrolimus, and/or polyclonal and monoclonal antilymphocyte agents (e.g., ALG and ATG).
4. Aetna considers ECP medically necessary for the treatment of graft-versus-host disease of an allogeneic bone marrow or stem cell transplant when the disease is refractory to standard immunosuppressive drug treatment.
5. Aetna considers the use of ECP experimental and investigational as a treatment for the following conditions because the effectiveness of this treatment for these diagnoses has not been established: s
 - Atopic dermatitis
 - Allograft rejection of solid organs other than the heart and lung
 - Bullous pemphigoid
 - Crohn's disease
 - Epidermolysis bullosa acquisita
 - Multiple sclerosis
 - Nephrogenic systemic fibrosis (previously known as nephrogenic fibrosing dermopathy)
 - Pemphigus vulgaris
 - Pityriasis rubra pilaris
 - Stage 0-p bronchiolitis obliterans syndrome
 - Systemic sclerosis (scleroderma)
 - Type 1 diabetes.

Policy History

▮ [Last Review](#): 05/14/2013
 Effective: 05/07/1998
 Next Review: 03/13/2014

▮ [Review History](#)
 ▮ [Definitions](#)

Additional Information

▮ [Clinical Policy Bulletin Notes](#)

Background

Photopheresis, also known as extracorporeal photochemotherapy (ECP), is an immunomodulatory technique based on pheresis of light-sensitive cells. Whole blood is removed from patients who have previously ingested the photosensitizing agent 8-methoxypsoralen (8-MOP) followed by leukapheresis and exposure of the 8-MOP containing leukocytes extracorporeally to ultraviolet-A light before their return to the patient. Two hours after an oral dose of photo-activatable drug, the patient undergoes leukopheresis. The lymphocytes are then exposed to UVA light within the photopheresis device and the photo-irradiated cells are re-infused into the patient.

Photopheresis was approved by the Food and Drug Administration (FDA) in 1988 for treatment of cutaneous T-cell lymphoma, and is considered standard therapy for the early to moderately advanced (stage III) erythrodermic variants of cutaneous T-cell lymphoma (e.g., mycosis fungoides, Sézary's syndrome). However, in a recent randomized controlled study, Child et al (2004) concluded that ECP is not effective in the treatment of plaque stage (1B/T2) mycosis fungoides even in patients with molecular evidence of a peripheral blood T-cell clone. This is in agreement with the findings of Zackheim (2003) who stated the results of ECP for early to moderately advanced erythrodermic mycosis fungoides are favorable. However, results in plaque and tumor stage disease are not impressive.

The Joint British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T-cell lymphomas recommended the use of ECP in patients with stage III mycosis fungoides/Sézary's syndrome.

Photopheresis is usually performed on 2 consecutive days at 4-week intervals with clinical evaluation at 6 months to determine response. Those who show clinical improvement are maintained on this treatment schedule until maximum clearing. An additional 6 months of treatment is typically given after which the patient is gradually weaned off therapy.

Photopheresis for the treatment of scleroderma and other autoimmune diseases is under investigation. The safety and efficacy of this treatment for scleroderma has not been established. Photopheresis, alone or in combination with immunosuppressive therapy, has also been used in the treatment of solid organ (e.g., heart, lung, and kidney) transplant rejection, graft-versus-host disease (GVHD), scleroderma, and other autoimmune diseases. This form of photochemotherapy induces a selective inhibition of the host response to foreign histocompatibility antigens and reverses allograft rejection after organ transplantation.

An assessment conducted by the BlueCross BlueShield Association Technology Evaluation Center (2001) concluded that ECP does not meet TEC criteria for autoimmune diseases, including: progressive systemic sclerosis (scleroderma); pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, or other autoimmune bullous (blistering) diseases; systemic lupus erythematosus; multiple sclerosis; psoriatic arthritis or psoriasis vulgaris; rheumatoid arthritis; type I diabetes; and other autoimmune diseases such as atopic dermatitis, juvenile dermatomyositis, or scleromyxedema.

Extracorporeal photopheresis is also being evaluated as a treatment for Crohn's disease. Available evidence is limited to case reports and small uncontrolled case series (Reinisch et al, 2001; Guariso et al, 2003). An assessment by the National Institute for Health and Clinical Excellence (2009) concluded: "[c]urrent evidence on extracorporeal photopheresis (ECP) for Crohn's disease is based on reports that include a very small number of patients. These reports describe no major safety issues but they provide little

evidence of efficacy. Therefore, this procedure should not be used outside the context of research."

Based upon an evidence review, the Centers for Medicare and Medicaid Services (CMS, 2006) concluded that ECP is reasonable and necessary for persons with acute cardiac allograft rejection whose disease is refractory to standard immunosuppressive drug treatment. Centers for Medicare and Medicaid Services also concluded that ECP is reasonable and necessary for persons with chronic GVHD whose disease is refractory to standard immunosuppressive drug treatment. There is evidence that photopheresis is effective in the treatment of heart, bone marrow and stem cell transplant rejection. Photopheresis has been reported to be as effective as conventional immunosuppressive agents in reducing rejection episodes in heart transplant recipients. It has also been demonstrated to be effective in treating steroid-resistant chronic GVHD following bone marrow or stem cell transplantation (Foss et al, 2005; Couriel et al, 2006; Bisaccia et al, 2006). By contrast, there is limited scientific evidence to determine the effectiveness of photopheresis in treating rejection of lung or kidney transplants .

Morrell et al (2010) reported that ECP is associated with a reduction in the rate of decline in lung function associated with progressive bronchiolitis obliterans syndrome (BOS). The authors retrospectively analyzed the efficacy and safety of ECP in 60 lung transplant recipients treated for progressive BOS at a single institution between 2000 and 2007. They reported that during the 6-month period before the initiation of ECP, the average rate of decline in forced expiratory volume in 1 second (FEV(1)) was -116.0 ml/month, but the slope decreased to -28.9 ml/month during the 6-month period after the initiation of ECP, and the mean difference in the rate of decline was 87.1 ml/month (95 % confidence interval [CI]: 57.3 to 116.9; $p < 0.0001$). The authors noted that FEV(1) improved in 25.0 % of patients after the initiation of ECP with a mean increase of 20.1 ml/month.

Haenssle and colleagues (2004) noted that pityriasis rubra pilaris (PRP) is a rare papulosquamous skin disease of unknown etiology that has been categorized into 5 clinical types based on age at onset, cutaneous features and prognosis. These investigators presented a patient with chronic exanthematic type II atypical adult PRP, whose skin status was significantly improved with monthly ECP. Various therapeutic regimens including narrow-band UV-B, bath PUVA therapy, systemic fumaric acid esters and systemic cyclosporin had failed. Oral retinoids could not be administered due to a type IIa hyper-lipoproteinemia with profound hepatic steatosis and elevated liver transaminases. The observed clinical benefit may encourage future clinical studies analyzing the clinical value of ECP in otherwise unresponsive cases of type II PRP.

Dall'Amico and Messina (2002) stated that ECP is a new type of photochemotherapy used for the treatment of oncological and autoimmune diseases. Additionally, recent reports indicated that this therapy is promising in both pediatric and adult patients who develop GVHD resistant to conventional protocols after bone marrow transplantation. These researchers reviewed 31 studies where ECP was used in the treatment of acute and chronic GVHD. A total of 76 (32 % female) acute GVHD patients have been considered in 11 series; 59 patients presented with skin involvement; 47 had liver involvement, and 28 had gastro-intestinal manifestations. Treatment duration ranged from 1 to 24 months. A regression of skin manifestations was observed in 83 % of the patients with a complete response in 67 %. A complete regression of liver and gut manifestations was reported in 38 % and 54 % of the patients, respectively. The overall patient survival was 53 %. Of the 43 patients alive, 8 developed chronic GVHD manifestations. The immunosuppressive therapy was discontinued in 28 % of cases and reduced in 46 %. A total of 204 (45 % female) chronic GVHD patients treated with ECP 1 to 110 months from transplantation have been considered in 20 series. A total of 128 patients presented with skin involvement; 84 with liver, 31 with lung, and 59 with oral manifestations. Treatment duration ranged from 3 to 40 months. A regression of skin manifestations was

observed in 76 % of patients with a complete response in 38 %. An improvement of liver and lung involvement was reported in 48 % and 39 % of the patients, respectively. Of the 59 patients with oral manifestations, an improvement was obtained in 63 % of cases. The overall patient survival was 79 %. Extracorporeal photopheresis is a non-aggressive treatment that may benefit patients with both acute and chronic GVHD who do not respond to standard immunosuppressive therapy.

Perfetti and associates (2008) examined the effects of ECP for the treatment of steroid refractory acute GVHD. Extracorporeal photopheresis was given to 23 patients with steroid-refractory acute GVHD (aGVHD, grade II (n = 10), III (n = 7) or IV (n = 6)). The median duration of ECP was 7 months (1 to 33) and the median number of ECP cycles in each patient was 10. Twelve patients (52 %) had complete responses. Eleven patients (48 %) survived and 12 died, 10 of GVHD with or without infections and 2 of leukemia relapse. The average grade of GVHD was reduced from 2.8 (on the first day of ECP) to 1.4 (on day +90 from ECP) ($p = 0.08$), and the average dose of intravenous methylprednisolone from 2.17 to 0.2 mg/kg/day ($p = 0.004$). Complete responses were obtained in 70, 42 and 0 % of patients, respectively, with grades II, III and IV aGVHD; complete responses in the skin, liver and gut were 66, 27 and 40 %. Patients treated within 35 days from onset of aGVHD had higher responses (83 versus 47 %; $p = 0.1$). A trend for improved survival was seen in grade III-IV aGVHD treated with ECP as compared to matched controls (38 versus 16 %; $p = 0.08$). The authors concluded that ECP is a treatment option for patients with steroid refractory aGVHD and should be considered early in the course of the disease. Moreover, the authors stated that "[t]he good results in patients receiving ECP, within 1 month from the onset of GVHD and when the severity does not exceed grade II-III may warrant a prospective trial to explore the role of photochemotherapy as upfront treatment of aGVHD".

A decision memorandum from the CMS concluded that there is insufficient evidence to support the use of ECP in pemphigus vulgaris and bullous pemphigoid (CMS, 2006).

Richmond and colleagues (2007) stated that nephrogenic systemic fibrosis (NSF), previously known as nephrogenic fibrosing dermopathy, is an idiopathic condition observed in patients with renal disease that is characterized by cutaneous sclerosis that can often result in contractures, pain, functional disability, and systemic complications. Recent reports have suggested a possible link with exposure to gadolinium. No current therapy has clearly demonstrated effectiveness for NSF, although case reports suggested that ECP may be of benefit. These researchers explored the plausibility of a gadolinium linkage with NSF and evaluated the effectiveness of ECP in the treatment of a cohort of patients with NSF (n = 8). Of the 8 patients, 6 had a history of arterial or venous thrombotic disease, and 7 had a documented exposure to gadolinium within 1 week to several months before onset of NSF. Specifically, all patients were exposed to gadodiamide. These investigators treated 5 of the patients with ECP. After a mean number of 34 treatment sessions over a mean of 8.5 months, 3 patients experienced a mild improvement in skin tightening, range of motion, and/or functional capacity. The authors concluded that their findings support the hypothesis that exposure to gadolinium, perhaps specifically gadodiamide, plays a role in the pathogenesis of NSF. They noted that larger epidemiologic studies will be needed to confirm this association. Furthermore, their experience suggest that, if used for extended periods, ECP might have some mild benefit for patients with NSF. They stated that larger, randomized, placebo-controlled trials of ECP should be performed to more specifically assess the benefit of ECP in the treatment of NSF.

Regarding the appropriate duration of ECP, an article from eMedicine recommends ECP weekly for 2 consecutive days each week, tapering to every other week until rejection resolves (Introcaso et al, 2007). A systematic review (Dall'Amico and Messina, 2002) assessed 31 studies of ECP for GVHD, and noted that treatment duration ranged from 3 to 40 months.

Shaughnessy et al (2010) stated that GVHD is partly mediated by host antigen-presenting cells (APCs) that activate donor T cells. Extracorporeal photopheresis can modulate APC function and benefit some patients with GVHD. These investigators reported the results of a study using ECP administered before a standard myeloablative preparative regimen intended to prevent GVHD. Grades II to IV acute GVHD developed in 9 (30 %) of 30 recipients of HLA-matched related transplants and 13 (41 %) of 32 recipients of HLA-matched unrelated or HLA-mismatched related donor transplants. Actuarial estimates of overall survival (OS) at day 100 and 1-year post transplant were 89 % (95 % CI: 78 to 94 %) and 77 % (95 % CI: 64 to 86 %), respectively. There were no unexpected adverse effects of ECP. Historical controls receiving similar conditioning and GVHD prophylaxis regimens but no ECP were identified from the database of the Center for International Blood and Marrow Transplant Research and multi-variate analysis indicated a lower risk of grades II to IV acute GVHD in patients receiving ECP ($p = 0.04$). Adjusted OS at 1 year was 83 % in the ECP study group and 67 % in the historical control group (relative risk 0.44; 95 % CI: 0.24 to 0.80) ($p = 0.007$). The authors concluded that these preliminary findings may indicate a potential survival advantage with ECP for transplant recipients undergoing standard myeloablative hematopoietic cell transplantation. Moreover, they stated that longer follow-up, larger sample sizes, and randomized comparisons to standard approaches are needed.

Kusztal et al (2011) stated that ECP is considered a promising immunomodulatory therapy of acute allograft rejection in organ transplantation and GVHD. These researchers investigated the biological responses of 10 patients who underwent kidney transplantation with ECP as prophylactic treatment. They received conventional immunosuppressive therapy plus ECP immediately after transplantation: 12 to 16 applications over the course of 2.5 months. ECP procedures were performed using an automated system for leukocyte separation and photo-activation with methoxsalen. All recipients were followed by estimated glomerular filtration rate (eGFR) and peripheral T, B, natural killer, T-regulatory (Treg) and dendritic cells (DC) counts and phenotypes. An acute rejection episode appeared in one control group recipient. The ECP group showed a positive trend to an higher GFR at months 3 (53 ± 11 versus 47.1 ± 9 ; $p = 0.17$) and 6 (67.5 ± 10 versus 53.6 ± 3 ; $p = 0.03$, Wilcoxon test). An increased percentage of Treg (CD3+ CD4+ CD25+) among the total CD3 cell count ($4.9 \% \pm 1 \%$ to $9.4 \% \pm 15 \%$) as well as inducible Treg (CD3+ CD8+ CD28-) was observed among CD3 cells ($3.3 \% \pm 3 \%$ to $11.8 \% \pm 8 \%$, $p = 0.025$) within 3 months of ECP treatment. A significant difference in the percentage of Treg was noted at month 3 (completed ECP) between the ECP and the control groups ($9.4 \% \pm 15 \%$ versus $3 \% \pm 1 \%$; $p = 0.01$). Addition of ECP to standard immunosuppression was associated with a significantly higher GFR at 6 months and with a significant increase in natural Treg among CD3 cells. The authors stated that these preliminary results are promising.

Gurcan and Ahmed (2011) noted that long-term remission in epidermolysis bullosa acquisita (EBA) patients is difficult to achieve. Patients who are resistant or develop side effects to conventional immunosuppressive therapy (CIST) have been treated with several other agents. These researchers reviewed the clinical outcome in patients treated with a single drug or combination, and determined if long-term remission can be induced. Data on 71 patients were analyzed. There are no controlled trials. The regimens used included dapsone, colchicine, mesalazine, cyclosporine, mycophenolic acid, intravenous immunoglobulin, rituximab, daclizumab, extracorporeal photochemotherapy, and plasmapheresis. The use of CIST, especially in wide spread and recalcitrant patients, usually does not produce a prolonged clinical remission and can have hazardous side effects. Intravenous immunoglobulin, rituximab and immunoabsorption have been successfully used in some, but the benefits from their use may require additional studies.

Lucid et al (2011) stated that ECP has been shown to be a promising treatment for chronic GVHD; however, only a few case reports are available that examine the

effectiveness of ECP for bronchiolitis obliterans (BO) after allogeneic stem cell transplantation (allo-SCT). Because of the poor response to traditional therapies, ECP has been explored as a possible therapeutic option for severe BO after allo-SCT. A total of 9 patients received ECP between July 2008 and August 2009 after a median follow-up of 23 months (range of 9 to 93 months) post-transplant. The primary indication for ECP was the development of BO in patients who had failed prior multi-drug regimens. The median number of drugs used for BO management before ECP was 5 (range of 2 to 7); this included immunosuppressive therapy. Six of 9 (67 %) patients responded to ECP after a median of 25 days (range of 20 to 958 days). No ECP-related complications occurred. ECP seemed to stabilize rapidly declining pulmonary function tests in about 2/3 of patients with severe and heavily pre-treated BO that developed after allo-SCT. The authors concluded that these findings support the need for a larger prospective study to confirm the impact of ECP on BO, and to consider earlier intervention with ECP to improve the outcome of BO after allo-SCT. Limitations of this study included its retrospective nature, small sample size, and short follow-up.

In a prospective study, Wolf et al (2012) examined the effect of a defined 20-week ECP protocol in patients with severe, refractory atopic dermatitis. The patient inclusion criteria included (i) disease duration of at least 1 year, (ii) "SCORing Atopic Dermatitis" (SCORAD; an objective clinical tool for assessing the severity (i.e., extent, intensity) of atopic dermatitis) greater than 45, and (iii) resistance to first-line therapy, including topical steroids, topical calcineurin inhibitors, and 1 form of phototherapy (UVA, UVB, or PUVA) or 1 second-line therapy, including systemic steroids or cyclosporine. A total of 10 patients (4 women and 6 men; age range of 29 to 61 years) were enrolled and treated with 2 sessions of standard ECP in 2-week intervals for 12 weeks and 4-week intervals thereafter until week 20. The patients' clinical status and response was determined by SCORAD at baseline and every 2 weeks, and quality of life was assessed every 4 weeks using SKINDEX, SF-36, and FACT scores. There was a statistically significant ($p = 0.015$) reduction of the mean SCORAD by 10.3 (95 % CI: 2.5 to 18.0) from 64.8 at baseline to 54.5 (i.e., 15.9 % reduction) at week 20. In a subset of patients (all of female sex), the relative reduction in SCORAD after ECP was more than 25 % at week 20. Improvement in quality of life measured by SKINDEX, SF-36, and FACT did not reach statistical significance. The authors concluded that they detected a small but significant therapeutic effect of ECP in patients with severe, refractory atopic dermatitis. The findings of this small study need to be validated by well-designed studies with larger sample size and longer follow-up.

Stage 0-p BOS (i.e., an average decline in FEV1 of 10 to 19 % of the basal value of 2 measurements at least 3 weeks apart) refers to a decline in lung function that is thought to be predictive of BOS, but does not establish the diagnosis of BOS (Riise et al, 2011).

Russo et al (2012) noted that since 1960, different classes of immunosuppressive drugs have been used in the post-transplant follow-up. Each is assessed for its effectiveness in preventing rejection but also on the basis of the many side effects induced by prolonged treatment. To reduce these side effects, continuous development of knowledge and medical technology to create cutting-edge therapies in the field is necessary. One of these is ECP, which is a useful therapeutic tool for the development of immunomodulation supported by CD8+ clone-specific cytotoxic lymphocytes. The T cells targeted by ECP are modified by photo-activation and seem to develop marked immunogenicity with no suppression of the immune response. Recent studies suggested the possible utility of ECP in the treatment of glomerulonephritis and in countering rejection after transplantation of organs including the kidney.

Lai et al (2012) stated that the fundamental role of antibodies in the development of acute graft rejection has been established recently. Antibody-mediated acute rejection may develop at any time during the post-renal transplant period. Several therapeutic approaches have been proposed in the last decades. However, there is no standardized

therapy. These researchers reported the Sapienza University experience of combined plasma treatment and high-dose intravenous immunoglobulin $\pm$ ECP. From January 2006 to September 2009, 6 patients were treated at Sapienza University. In 5 cases (83 %) complete regression of the acute rejection was observed, followed by stable renal function (median creatinine value at 1-year follow-up: 1.5 mg/dL). No adverse events were reported. The authors concluded that this approach seems to give good results in terms of graft survival and procedure safety. Moreover, they stated that further studies on a larger number of patients are needed to confirm the validity of these findings. Furthermore, comparison between the authors' protocol and other treatments is necessary.

Benden et al (2012) noted that lung transplantation has evolved as an accepted therapy in selected adults and children with end-stage lung diseases. Outcomes following lung transplantation have improved in the recent era with a 5-year survival of greater than 70 % and an overall good functional status of surviving recipients. Many of the advances have been achieved by the use of modern immunosuppressive agents. To date, multiple strategies exist that may be employed when utilizing immunosuppression. These agents can be used in a variety of roles that may include induction, maintenance or rescue therapy, many of which are illustrated in this review including the current evidence to support their use. Infections in lung transplant recipients remain a significant cause of morbidity and mortality. Special considerations are required with the substantial burden of chronic infection in candidates with cystic fibrosis lung disease before transplantation. Furthermore, recent progress and advances in prevention and treatment of post-transplantation infectious complications were detailed. Chronic lung allograft dysfunction remains to be the burden of lung transplantation in the long-term. Unfortunately, there is no well-established therapy to address it. However, therapy attempts include change/augmentation of immunosuppression, use of neomacrolides and ECP, all of which were reviewed in detail.

Kaloyannidis and Mallouri (2012) noted that over the last decades significant advances have been made in the field of donor selection, alternative transplant sources, immunosuppressive treatment and supportive care, as well as in the better understanding of the immunobiology of allogeneic hematopoietic stem cell transplantation (alloTx). Nevertheless, several factors still affect unfavorably the outcome of the procedure. Graft-versus-host disease remains the leading cause of morbidity, non-relapse mortality and treatment failure post alloTx. So far, steroids are the widely used 1st-line treatment for GVHD achieving considerable response rate however, patients who fail to respond to the initial therapy have a dismal prognosis and no standard treatment is well-established for them to date. In recent years, ECP has been proposed as a safe and effective treatment for steroid-refractory GVHD. Overall responses of 75 % have been reported in the cutaneous and mucosal involvement and 45 to 65 % in other organ manifestations (e.g., lung, liver and intestinal), allowing reduction and even discontinuation of steroids, thus contributing towards a significant reduction of morbidity. Although the mechanism of action of ECP is not fully understood, it seems that it has an immunomodulatory rather than an immunosuppression effect and induces immunotolerance, preserving the beneficial graft-versus-tumor effect. Given these very promising results in steroid-refractory or steroid-dependent GVHD, currently, ECP is being investigated as both first-line and prevention therapy also.

In a review on "Bronchiolitis obliterans after allo-SCT: Clinical criteria and treatment options", Uhlving and colleagues (2012) stated that "though several studies have been performed in patients with BO after HSCT and lung transplantation, the studies are difficult to interpret because of the heterogeneity in the treatment schedules, diagnostic criteria and response assessment criteria. A prospective study randomized study of extracorporeal photopheresis treatment performed by Flower et al revealed a significant improvement of cGVHD in the skin, and indicated a steroid sparing effect on cGVHD in

general. No effect on lung function parameters was noted Solid evidence regarding the efficacy of the various available treatment modalities in BO is still sparse".

On April 30, 2012, a National Coverage Determination (NCD) by the Centers for Medicare & Medicaid Services stated that ECP for the treatment of bronchiolitis obliterans syndrome (BOS) following lung allograft transplantation will be covered only when ECP is provided under a clinical research study that meets criteria. An accompanying decision memorandum (CMS, 2012) stated that the evidence is insufficient to conclude that, in Medicare beneficiaries with BOS developing after lung allograft transplantation refractory to standard immunosuppressive therapy, ECP will improve patient centered health outcomes. However, based on its previously published criteria for considering CED, CMS concluded that evidence of basic safety, potential for patient-centered health outcome improvement, and demonstrated difficulty of conducting appropriate clinical trials are sufficient in combination to persuade CMS to propose coverage for ECP therapy for BOS after lung allograft transplantation within approved clinical research studies.

CPT Codes / HCPCS Codes / ICD-9 Codes

CPT codes covered if selection criteria are met:

36522

ICD-9 codes covered if selection criteria are met:

202.10 - 202.18 Mycosis fungoides

202.20 - 202.28 Sezary's disease

279.50 - 279.53 Graft-versus-host disease

996.83 Complications of transplanted organ; heart

996.84 Complication of transplanted organ; lung

996.85 bone marrow

V42.1 Organ or tissue replaced by transplant; heart

V42.81 other specified organ or tissue, bone marrow

V42.82 other specified organ or tissue, peripheral stem cells

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

242.00 - 242.01 Toxic diffuse goiter

245.2 Chronic lymphocytic thyroiditis

250.00 - 250.93 Diabetes mellitus

255.41 - 255.42 Corticoadrenal insufficiency

281.0 Pernicious anemia

283.0 Autoimmune hemolytic anemias

287.0 Allergic purpura

340 Multiple sclerosis

358.00 - 358.01 Myasthenia gravis

446.21 Goodpasture's syndrome

555.0 - 555.9 Regional enteritis [Crohn's]

691.8 Other atopic dermatitis and related conditions

694.4	Pemphigus
694.5	Pemphigoid
696.4	Pityriasis rubra pilaris
710.0	Systemic lupus erythematosus
710.1	Systemic sclerosis [scleroderma]
710.2	Sicca syndrome
710.4	Polymyositis
714.0 - 714.9	Rheumatoid arthritis and other inflammatory polyarthropathies
757.39	Other specified congenital anomaly of skin [epidermolysis bullosa acquisita]
996.81	Complications of transplanted organ, kidney
996.82	Complications of transplanted organ, liver
996.86	Complications of transplanted organ, pancreas
996.87	Complications of transplanted organ, intestine
V42.0	Organ or tissue replaced by transplant, kidney
V42.6	Organ or tissue replaced by transplant, lung
V42.7	Organ or tissue replaced by transplant, liver
V42.83	Organ or tissue replaced by transplant, pancreas
V42.84	Organ or tissue replaced by transplant, intestines

The above policy is based on the following references:

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MEDICAL POLICY

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Plasma Exchange

Number 8.02.02

Effective Date July 24, 2013

Revision Date(s) 07/08/13; 02/11/13; 07/10/12; 06/13/11; 04/13/10; 06/09/09; 08/08/06; 06/14/05; 05/11/04; 05/13/03; 08/13/02; 11/13/01

Replaces 8.02.500

Policy

[\[TOP\]](#)

Plasma exchange is considered **medically necessary** for the conditions listed below:

Autoimmune

- Severe multiple manifestations of mixed cryoglobulinemia (MC) such as cryoglobulinemic nephropathy, skin ulcers, sensory motor neuropathy, and widespread vasculitis in combination with immunosuppressive treatment;
- Catastrophic antiphospholipid syndrome (CAPS).

Hematologic

- ABO incompatible hematopoietic progenitor cell transplantation;
- Hyperviscosity syndromes associated with multiple myeloma or Waldenstrom's macroglobulinemia;
- Idiopathic thrombocytopenic purpura in emergency situations;
- Thrombotic thrombocytopenic purpura (TTP);
- Atypical hemolytic-uremic syndrome;
- Post-transfusion purpura;
- HELLP syndrome of pregnancy (a severe form of preeclampsia, characterized by hemolysis [H], elevated liver enzymes [EL], and low platelet [LP] counts);
- Myeloma with acute renal failure.

Neurological

- Acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome [GBS]; severity grade 1–2 within 2 weeks of onset; severity grade 3–5 within 4 weeks of onset; and children younger than 10 years -old with severe GBS);
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP);
- Multiple sclerosis (MS); acute fulminant central nervous system (CNS) demyelination
- Myasthenia gravis in crisis or as part of preoperative preparation;
- Paraproteinemia polyneuropathy; IgA, IgG.

Renal

- Anti-glomerular basement membrane disease (Goodpasture's syndrome); ANCA [Antineutrophil cytoplasmic antibody] -associated vasculitis [e.g., Wegener's granulomatosis [also known as granulomatosis with polyangitis (GPA)] with associated renal failure;
- Dense deposit disease with factor H deficiency and/or elevated C3 Nephritic factor.

Transplantation

- ABO incompatible solid organ transplantation;
- Kidney;
- Heart (infants);
- Renal transplantation: antibody mediated rejection; HLA [human leukocyte antigen] desensitization;
- Focal segmental glomerulosclerosis after renal transplant.

Plasma exchange is considered **investigational** in all other conditions, including, but not limited, to the following:

- ABO -incompatible solid organ transplant; liver;
- Acute disseminated encephalomyelitis;
- Acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome) in children younger than 10 years -old with mild or moderate forms;
- Acute liver failure;
- Amyotrophic lateral sclerosis;
- ANCA [antineutrophil cytoplasmic antibody]-associated rapidly progressive glomerulonephritis (Wegener's granulomatosis or GPA without renal failure);
- Aplastic anemia;
- Asthma;
- Autoimmune hemolytic anemia; warm autoimmune hemolytic anemia; cold agglutinin disease;
- Chronic fatigue syndrome;
- Coagulation factor inhibitors;
- Cryoglobulinemia; except for severe mixed cryoglobulinemia, as noted above;
- Dermatomyositis and polymyositis;
- Focal segmental glomerulosclerosis (other than after renal transplant);
- Heart transplant rejection treatment;
- Hemolytic uremic syndrome (HUS); typical (diarrheal-related);
- Idiopathic thrombocytopenic purpura; refractory or non-refractory;
- Inclusion body myositis;
- Lambert-Eaton myasthenic syndrome;
- Multiple sclerosis; chronic progressive or relapsing remitting;
- Mushroom poisoning;
- Myasthenia gravis with anti-MuSK antibodies;
- Overdose and poisoning (other than mushroom poisoning);
- Paraneoplastic syndromes;
- Paraproteinemia polyneuropathy; IgM
- Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)
- Pemphigus vulgaris;
- Phytanic acid storage disease (Refsum's disease);
- POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes);
- Psoriasis;
- red blood cell alloimmunization in pregnancy;
- Rheumatoid arthritis;
- Sepsis;
- Scleroderma (systemic sclerosis);
- Stiff person syndrome;
- Sydenham's chorea (SC);
- Systemic lupus erythematosus (including SLE [systemic lupus erythematosus] nephritis); and
- Thyrotoxicosis
- Hyperviscosity syndromes with renal failure (other than associated with multiple myeloma or Waldenstrom's macroglobulinemia).

Related Policies

[\[TOP\]](#)

7.03.05	Small Bowel/Liver and Multivisceral Transplant
7.03.509	Solid Organ Transplants
7.03.510	Isolated Small Bowel Transplant
8.01.17	Hematopoietic Stem-Cell Transplantation Multiple Myeloma
8.01.25	Hematopoietic Stem-Cell Transplantation for Autoimmune Diseases
8.01.36	Extracorporeal Photopheresis
8.01.503	Immune Globulin Therapy
8.02.04	Low-Density Lipid Apheresis

Policy Guidelines

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Patients receiving plasma exchange (PE) as a treatment of CIDP should meet the diagnostic criteria for chronic inflammatory demyelinating polyneuropathy (CIDP), which are included in an Appendix to this policy.

The use of PE in patients with acute, life-threatening complications of chronic autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus (SLE), may need to be considered on an individual basis. An example of such a situation would be the development of a severe vasculitis, in which it is hoped that the use of PE can acutely lower the level of serum autoantibodies until an alternate long-term treatment strategy can be implemented. However, in these situations, the treatment goals and duration of treatment with PE need to be clearly established prior to its initiation; without such treatment goals, the use of an acute short-term course of PE may insidiously evolve to a chronic use of PE with uncertain benefit.

In 2003, CPT introduced a variety of CPT codes that describe different types of apheresis procedures. CPT codes 36514 specifically describe “therapeutic apheresis, for plasma pheresis.”

Description

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Plasma exchange (PE) is a procedure in which the plasma is isolated, then discarded and replaced with a substitution fluid such as albumin. Plasma exchange is a nonspecific therapy, since the entire plasma is discarded. PE has been used in a wide variety of acute and chronic conditions, as well as in the setting of solid organ transplantation.

Background

The terms therapeutic apheresis, plasmapheresis, and plasma exchange (PE) are often used interchangeably, but when properly used denote different procedures. The American Society for Apheresis (ASFA) definitions for these procedures are as follows:

Apheresis: A procedure in which blood of the patient or donor is passed through a medical device which separates out one or more components of blood and returns remainder with or without extracorporeal treatment or replacement of the separated component.

Plasmapheresis: A procedure in which blood of a patient or the donor is passed through a medical device which separates out plasma from the other components of blood and the plasma is removed (i.e., less than 15% of total plasma volume) without the use of replacement solution.

Plasma exchange: A therapeutic procedure in which blood of the patient is passed through a medical device which separates out plasma from other components of blood, the plasma is removed and replaced with a replacement solution such as colloid solution (e.g., albumin and/ or plasma) or a combination of crystalloid/colloid solution.

This policy addresses only plasma exchange as a therapeutic apheresis procedure.

The rationale for PE is based on the fact that circulating substances, such as toxins or autoantibodies, can accumulate in the plasma. Also, it is hypothesized that removal of these factors can be therapeutic in certain situations. PE is essentially a symptomatic therapy, since it does not remove the source of the pathogenic factors. Therefore the success of PE will depend on whether the pathogenic substances are accessible through the circulation and whether their rate of production and transfer to the plasma component can be adequately addressed by PE. For example, PE can rapidly reduce levels of serum autoantibodies; however, through a feedback mechanism, this rapid reduction may lead to a rebound overproduction of the same antibodies. This rebound production of antibodies is thought to render the replicating pathogenic clone of lymphocytes more vulnerable to cytotoxic drugs; therefore, PE is sometimes used in conjunction with cyclophosphamide.

Applications of PE can be broadly subdivided into two general categories: 1) acute self-limited diseases, in which PE is used to acutely lower the circulating pathogenic substance; and 2) chronic diseases, in which there is ongoing production of pathogenic autoantibodies. Because PE does not address underlying pathology, and, due to the phenomenon of rebound antibody production, its use in chronic diseases has been more controversial than in acute self-limited diseases.

In addition, plasmapheresis has been used in the setting of solid organ transplantation. It has been used as a technique to desensitize high-risk patients prior to transplant and also as a treatment of antibody-mediated rejection reaction (AMR) occurring after transplant. Prior to transplant, plasmapheresis has been most commonly used to desensitize patients receiving an ABO mismatched kidney, often in combination with a splenectomy. As a treatment of AMR, plasmapheresis is often used in combination with intravenous immunoglobulin (IVIg) or anti-CD-20 therapy (i.e., Rituxan).

Scope

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Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply.

Benefit Application

[\[TOP\]](#)

N/A

Rationale

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This policy was originally created in 1995 and was updated regularly with searches of the MEDLINE database. The most recent literature search was performed for the period April 15, 2012 through March 21, 2013. Following is a summary of the key literature to date:

Autoimmune Diseases

One potential type of evidence in support of the clinical effectiveness of plasma exchange (PE) in treating autoimmune diseases is the identification of a pathogenic component of plasma that is reliably eliminated by plasmapheresis. (1) Although many laboratory abnormalities are associated with autoimmune connective tissue diseases, it is unclear which, if any, cause the clinical manifestations of the disease. Furthermore, it is not known to what extent plasma levels parallel clinical disease. For example, in many of the controlled trials discussed as follows, PE reliably reduced circulating autoantibodies and immune complexes, but without demonstrable clinical benefit. It may be that the patient had already suffered irreversible damage or that the pathogenesis of the disease was a local process unrelated to circulating factors. Over the past 10 years, randomized trials of PE have been conducted and, in general, have shown a lack of effectiveness as treatment of chronic autoimmune diseases. Clinical results of randomized trials of plasmapheresis for specific chronic autoimmune diseases are discussed here.

Systemic Lupus Erythematosus

Reporting on the results of a randomized controlled trial (RCT), Lewis and colleagues concluded that PE had no benefit in patients with systemic lupus and glomerulonephritis compared to a standard therapy regimen of prednisone and cyclophosphamide. (2) Plasmapheresis has also been investigated as a technique to improve the effectiveness of cyclophosphamide therapy. For example, it is thought that the acute lowering of pathogenic autoantibodies with plasmapheresis may result in their rebound production. It is hoped that the pathogenic lymphocytes would be more sensitive to cyclophosphamide at this point. Danieli and colleagues reported on a prospective nonrandomized trial of 28 patients with proliferative lupus nephritis; 12 underwent synchronized plasmapheresis and pulse cyclophosphamide therapy, while the remaining 16 underwent cyclophosphamide alone. (3) While plasmapheresis was associated with a decreased time to remission of renal disease, at the end of the 4-year follow-up, there was no difference in outcome.

Multiple Sclerosis (MS)

There have been several RCTs of PE in patients with MS that have reported inconclusive results. Khatri and colleagues studied 54 patients with chronic progressive MS randomized to receive sham or true PE. (4) The degree of improvement in the PE group was greater than that in the control group. Weiner et al. reported on a study that randomized patients with acute attacks of MS to receive either PE or sham treatments; there was no statistical difference in improvement between groups, although patients receiving PE did have a faster recovery rate from acute attacks. (5) A Canadian trial randomized 168 patients with progressive MS to receive either PE or immunosuppressive therapy. (6) There were no significant differences in the rates of treatment failures between groups.

Lambert-Eaton Myasthenic Syndrome (LEMS) and Other Paraneoplastic Syndromes

Paraneoplastic neuromuscular syndromes are characterized by the production of tumor antibodies that cross-react with the patient's nervous system tissues. The Lambert-Eaton myasthenic syndrome (LEMS), characterized by proximal muscle weakness of the lower extremities and associated most frequently with small cell lung cancer, is the most common paraneoplastic syndrome. The presumed autoimmune nature of LEMS and other paraneoplastic syndromes led to the use of a variety of immunomodulatory therapies, including PE. However, there are minimal data in the published literature and no controlled trials. The largest case series focusing on LEMS was reported by Tim and colleagues and included 73 patients with LEMS, 31 of whom were found to have lung cancer. (7) Although detailed treatment strategies are not provided, 19 underwent plasmapheresis, with 27% reporting a moderate to marked response. However, the improvement after plasmapheresis, even when marked was only transient. Patients also received other therapies, for example, various chemotherapy regimens for the underlying lung cancer. In addition, 53 of the 73 patients received 3, 4 diaminopyridine, with 79% reporting marked or moderate responses. A small RCT of 3, 4 diaminopyridine has also reported positive results, confirming other anecdotal reports. (8) Anderson and colleagues reported on a case series of 12 patients with paraneoplastic cerebellar degeneration. Although plasmapheresis was associated with an acute drop in the autoantibody titer, only 2 patients showed a minor improvement in neurologic symptoms. (9)

Rheumatoid Arthritis

In 1983, Dwosh and colleagues reported on 26 patients with chronic rheumatoid arthritis randomized in a crossover design to either true or sham PE. The authors concluded that PE did not have any clinical benefit despite impressive laboratory changes. (10)

Polymyositis/Dermatomyositis

Miller and colleagues conducted a randomized trial of PE in the treatment of 39 patients with polymyositis and dermatomyositis and found that it was no more effective than sham pheresis. (11)

Pemphigus

Pemphigus is an autoimmune blistering skin disease that is characterized by serum antibodies that bind to squamous epithelia. Steroids or other immunosuppressants are the most common forms of treatment, but the high doses of steroids can produce significant side effects. Guillaume and colleagues reported on a study of 40 patients with pemphigus randomized to receive either prednisone alone or prednisone plus plasmapheresis. (12) The goal of the study was to determine whether plasmapheresis could reduce the

required dose of steroids, thus limiting its toxicity. Unfortunately, disease control in the two groups was the same, and the authors concluded that plasmapheresis in conjunction with low-dose steroids is not effective in treating pemphigus.

StiffMan (aka Stiff Person) Syndrome

Stiff man syndrome is an autoimmune disorder characterized by involuntary stiffness of axial muscles and intermittent painful muscle spasm. Stiff man syndrome may be idiopathic in nature or seen in association with thymoma, Hodgkin's disease, and small cell lung; colon; or breast cancer. The mainstay of treatment of stiff man syndrome is diazepam. The published literature regarding plasmapheresis consists of small case series and anecdotal reports. (13-15)

Cryoglobulinemia

There are several types of cryoglobulinemia. Type I is associated with hematologic disorders. Types II and III are considered mixed cryoglobulins. Mixed cryoglobulin syndrome is a consequence of immune-complex mediated vasculitis and may be associated with infectious and systemic disorders (e.g., hepatitis C virus). In 2010, Rockx and Clark published a review of studies evaluating PE for treating cryoglobulinemia that included at least 5 patients. (16) They identified 11 studies with a total of 156 patients. The authors concluded, "The quality and variability of the evidence precludes a meta-analysis or even a systematic analysis. However, these studies weakly support the use of plasma exchange largely on a mechanistic basis."

Hematologic

Thrombotic Thrombocytopenic Purpura (TTP) and Haemolytic Uraemic Syndrome (HUS)

Once considered distinct syndromes, TTP and HUS are now considered different manifestations of the same disease process, i.e., thrombotic microangiopathy. In 2009, a systematic review evaluated the benefits and harms of different interventions for HUS and TTP (separately). (17) Interventions compared with placebo or supportive therapy or a comparison of two or more interventions. Interventions examined included heparin, aspirin/dipyridamole, prostanoids, ticlopidine, vincristine, fresh frozen plasma (FFP) infusion, plasmapheresis with fresh frozen plasma (FFP), systemic corticosteroids, Shiga toxin -binding agents, or immunosuppressive agents. For TTP, 6 RCTs (n=331 participants) were identified evaluating PE with FFP as the control. Interventions tested included antiplatelet therapy (APT) plus PE with FFP, FFP transfusion, and PE with cryosupernatant plasma. (CSP). Two studies compared plasma infusion (PI) to PE with FFP and showed a significant increase in failure of remission at 2 weeks (risk ratio [RR]: 1.48) and all-cause mortality (RR: 1.91) in the PI group. The authors concluded that PE with fresh frozen plasma/FFP is the most effective treatment available for TTP. Seven RCTs included children with HUS. None of the assessed interventions was superior to supportive therapy alone for all-cause mortality, neurological/extrarenal events, renal biopsy changes, proteinuria, or hypertension at the last follow-up visit. Bleeding was significantly higher in those receiving anticoagulation therapy compared to supportive therapy alone (RR: 25.89). For patients with HUS, supportive therapy including dialysis was the most effective treatment. All studies in HUS have been conducted in the diarrheal form of the disease. There were no RCTs evaluating the effectiveness of any interventions on patients with atypical HUS who have a more chronic and relapsing course. A recent review article by Noris and Remuzzi describes the data supporting use of PE in the atypical form of this disease, with results showing remission in up to 60% of patients. (18)

Because the available evidence for patients with typical HUS shows supportive therapy, including dialysis, to be the most effective treatment, all studies in HUS have been conducted with patients with the diarrheal (typical) form of the disease; the use of PE for the treatment of typical HUS is inadequate to draw clinical conclusions. PE for HUS was considered medically necessary in previous updates. PE remains medically necessary for atypical HUS.

Idiopathic thrombocytopenic purpura (ITP)

ITP is an acquired disease of either adults or children characterized by the development of autoantibodies to platelets. Management of acute bleeding due to thrombocytopenia typically involves immediate platelet transfusion, occasionally in conjunction with a single infusion of intravenous immunoglobulin (IVIg). PE has been occasionally used in emergency situations.

Post-transfusion purpura

Post-transfusion purpura is a rare disorder characterized by an acute severe thrombocytopenia occurring about 1 week after a blood transfusion in association with a high titer of anti-platelet alloantibodies. Due to its rapid effect, PE is considered the initial treatment of choice.

HELLP syndrome of pregnancy

The HELLP syndrome of pregnancy (characterized by hemolysis [H], elevated liver enzymes [EL], and low platelet [LP] counts) is a severe form of preeclampsia, characterized by hemolysis, elevated liver enzymes, and low platelet counts. The principal form of treatment is delivery of the fetus. However, for patients with severe thrombocytopenia, PE may be indicated if the fetus cannot safely be delivered, or if the maternal thrombocytopenia persists into the postnatal period.

Neurological

Guillain-Barré Syndrome (GBS)

Guillain-Barré syndrome is an acute demyelinating neuropathy whose severity is graded on a scale of 1–5 (the disability scale is summarized in the Appendix to this policy). In 2012, The Cochrane Collaboration published an updated systematic review of the evidence concerning the efficacy of PE for treating GBS. (19) Six eligible trials (n=649) were identified comparing PE versus supportive treatment alone. No additional trials were published since the 2002 review. The Primary outcome measures of the review included time to recover walking with aid and time to onset of motor recovery in mildly affected patients. A pooled analysis of data from 3 trials found that PE significantly increased the proportion of patients who recovered the ability to walk with assistance after 4 weeks (RR: 1.60, 95% confidence interval [CI]: 1.19 to 2.15). Data on time to onset of motor recovery were not pooled. Pooled analyses found that PE led to significant improvement in secondary outcomes including reduced time to recover walking without aid, increased likelihood of full muscle strength recovery and reduced likelihood of severe motor sequelae. However, there was a significantly higher risk of relapse in the group that received PE compared to supportive treatment alone (RR: 2.89, 95% CI: 1.05 to 7.93, 6 trials).

A 2007 systematic review evaluated the available randomized trials of immunotherapy to treat GBS. (20) In 4 trials with severely affected adult participants (n=585), those treated with plasma exchange (PE) improved significantly more on the disability scale 4 weeks after randomization than those who were not (weighted mean difference [WMD]: -0.89; range: -1.14 to -0.63). In 5 trials (n=582), the improvement on the disability grade scale with IVIg was very similar to that with PE, WMD: -0.02 (range: -0.25 to 0.20). There was also no significant difference between IVIg and PE for any of the other outcome measures. There was 1 trial that included patients (n=91) with the mild form of GBS who were able to walk unaided at enrollment. Patients were randomized to receive either two sessions of PE in 3 days or supportive care. The number of patients with one or more grades of improvement at 1 month was significantly greater, 26/45 in the treated compared to the control group, 13/45. Fewer patients in the PE-treated group had clinical deterioration (4%) as compared to the control group (39%) or required ventilation; PE group (2%) versus the control group (13%). In 1 trial (n=148), following PE with IVIg, did not produce significant extra benefit. Limited evidence from 3 open trials in children suggested that IVIg hastens recovery compared with supportive care alone. None of the treatments significantly reduced mortality. The authors concluded that “since approximately 20% of patients die or have persistent disability despite immunotherapy, more research is needed to identify better treatment regimens and new therapeutic strategies.”

In 2003, a report of the Quality Standards Subcommittee of the American Academy of Neurology (AAN), *Practice parameter: Immunotherapy for Guillain-Barré syndrome*, was published. (21) The following are the key findings: 1) treatment with PE or IVIg hastens recovery from Guillain-Barré syndrome; 2) combining the 2 treatments is not beneficial; and 3) steroid treatment given alone is not beneficial. The AAN's recommendations are: 1) PE is recommended for nonambulant adult patients with GBS who seek treatment within 4 weeks of the onset of neuropathic symptoms (PE should also be considered for ambulant patients examined within 2 weeks of the onset of neuropathic symptoms); 2) IVIg is recommended for nonambulant adult patients with GBS within 2 or possibly 4 weeks of the onset of neuropathic symptoms (the effects of PE and IVIg are equivalent); 3) corticosteroids are not recommended for the management of GBS; 4) sequential treatment with PE followed by IVIg, or immunoabsorption followed by IVIg is not recommended for patients with GBS; and 5) PE and IVIg are treatment options for children with severe GBS.

A 2011 RCT from Iran addresses PE for treating young children with severe GBS. (22) The study included 41 children with GBS who required mechanical ventilation and had muscle weakness for no more than 14 days. Patients were randomized to receive PE (n=21) or intravenous immunoglobulin (IVIg) (n=20). Mean age of the patients was 96 months in the PE group and 106 months in the IVIg group. Duration of ventilation, the primary outcome, was a mean of 11 days (standard deviation [SD]=1.5) in the PE group and 13 days (SD=2.1) in the IVIg group, p=0.037. Duration of stay in the intensive care unit, a secondary outcome, was 15.0 days (SD=2.6 days) in the PE group and 16.5 days (SD=2.1 days) in the IVIg group; p=0.94.

In conclusion, the available evidence is sufficient regarding PE for the treatment of patients with all severity grades of GBS. This therapy has a beneficial impact on net health outcome for all severity grades. The published studies are insufficient regarding PE for treatment of GBS in the pediatric population. However, based on limited published data, as well as extrapolated data from studies in adults and clinical input, PE may be considered as a treatment option for children younger than 10years -old with severe GBS.

Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

A 2012 Cochrane review by Mehnidiratta and Hughes identified 2 randomized trials on PE for CIDP. (23) Both trials were considered to be of high quality, but both had small sample sizes. One trial with 29 patients used a parallel design and compared PE to sham treatment. The other study included 15 patients and used a cross-over design to compare PE and sham treatment. A pooled analysis of data from the 2 trials found a statistically significantly greater improvement in impairment after 4 weeks with PE versus sham (mean difference 31 points on the Neuropathy Impairment Score, 95% CI: 16 to 45 points). The scale ranges from 0 (normal) to 280 (maximally affected). Data on other outcomes were not suitable for pooled analysis.

Acute Fulminant Central Nervous System (CNS) Demyelination

The policy statement, which suggests that plasmapheresis may be considered medically necessary in patients with acute fulminant CNS demyelination, is based on the results of a randomized, double-blinded trial, in which 22 patients with MS or other acute idiopathic inflammatory demyelinating diseases of the CNS were enrolled a minimum of 14 days after having failed to respond to at least 5 days of high-dose corticosteroids. (24) Patients were randomized to receive either 7 real or sham PE procedures over a 14-day period. The primary outcome was a targeted neurologic deficit (i.e., aphasia, cognitive dysfunction, etc.). Overall, moderate to marked improvement of the targeted outcome was obtained in 42% of the treatment group, compared to only 6% in the placebo group.

Paraproteinemic Polyneuropathies

A randomized, double-blinded trial compared PE to sham treatment in 39 patients with monoclonal gammopathy of undetermined significance (MGUS)-associated polyneuropathy. (25) After twice weekly PE for 3 weeks, the treatment group reported improvements in neurologic function in the IgG and IgA groups but not the IgM MGUS groups. In addition, those from the sham group who were later crossed over to the PE group also reported improvement.

Myasthenia Gravis (MG)

A randomized trial from China was published in 2009. (26) Liu and colleagues assigned 40 patients with late-onset myasthenia gravis to treatment with double-filtration plasmapheresis (n=15), immunoadsorption (IA) (n=10), or intravenous immune globulin (n=15). Treatment was clinically effective, defined as at least a 50% improvement in the relative symptom score, in 12 of 15 (80%) of the plasmapheresis group, 7 of 10 (70%) in the immunoadsorption group, and 6 of 15 (40%) of the immune globulin group. The clinical efficacy rate was significantly higher in both the plasmapheresis and immunoadsorption groups compared to the immune globulin group ($p < 0.05$). Findings were similar for other outcomes; the study was limited by the small sample size.

A 2011 RCT from Germany randomized patients with myasthenic crisis to treatment with PE (n=10) or immunoadsorption (IA) (n=9). (27) In both groups, 3 apheresis treatments were performed within 7 days; patients could have additional treatments if needed. A total of 16/19 (84%) of patients, 8 in each group, completed the study and were included in the efficacy analysis. The mean number of treatments was 3.5 in the PE group and 3.4 in the IA group ($p > 0.05$). The primary outcome was change in the modified clinical score (maximum of 3 points) on day 14 after the last treatment. The baseline modified clinical score was 2.6 in the PE group and 2.5 in the IA group. At day 14, score improvement was 1.6 points in the PE group and 1.4 points in the IA group; $p > 0.05$. Within the 180 days after treatment, 1 patient in the PE group and 3 patients in the IA group experienced another myasthenic crisis; the number of events was too small for meaningful statistical analysis for this outcome. There were no statistically significant differences in outcomes in this study, but the sample was very small and the study was probably underpowered.

Renal

Rapidly Progressive Glomerulonephritis (RPGN)

RPGN is a general term describing the rapid loss of renal function in conjunction with the finding of glomerular crescents on renal biopsy specimens. There are multiple etiologies of RPGN including vasculitis, the deposition of anti-glomerular basement membrane (GBM) antibodies as seen in Goodpasture's syndrome, or the deposition of immune complexes as seen in various infectious diseases or connective tissue diseases. PE has long been considered a treatment alternative in immune-mediated RPGN. However, there have been few controlled clinical trials published, and their interpretation is difficult due to the small number of patients, choice of intermediate outcomes (i.e., the reduction in antibody levels as opposed to more direct patient outcomes), and heterogeneity in patient groups. (28) Aside from cases of Goodpasture's disease, the rationale for PE in idiopathic RPGN is not as strong, due to the lack of an identifiable immune component. Studies of PE in this population have not demonstrated a significant improvement in outcome compared to the use of pulse steroid therapy. (29)

Antineutrophil cytoplasmic antibody (ANCA)-associated Vasculitis

In 2011, Walsh and colleagues published a meta-analysis of studies on plasma exchange in adults with the diagnosis of either idiopathic renal vasculitis or rapidly progressive glomerulonephritis. (30) A total of 9 trials including 387 patients were identified. The clinical populations in the studies were somewhat ill-defined, but most patients appeared to have ANCA-associated vasculitis. In a pooled analysis of study findings, there was a significantly lower risk of end-stage renal disease in patients treated with adjunctive PE compared to standard care alone (RR 0.64, 95% CI: 0.47 to 0.88). The risk of death did not differ significantly in the 2 groups (RR:1.01, 95% CI: 0.71-1.40).

A relatively large RCT, included in the Walsh et al. meta-analysis, was published in 2007 by Jayne and colleagues. (31) This was a multicenter trial conducted on behalf of the European Vasculitis Study Group. The study investigated whether the addition of PE was more effective than intravenous methylprednisolone. Patients (n=137) with a new diagnosis of ANCA-associated systemic vasculitis confirmed by renal biopsy and serum creatinine greater than 500 micromol/L (5.8 mg/dL) were randomly assigned to receive seven PEs (n=70) or 3,000 mg of intravenous methylprednisolone (n=67). Both groups received oral cyclophosphamide and oral prednisolone. The primary endpoint was dialysis independence at 3 months. Secondary endpoints included renal and patient survival at 1 year and severe adverse event rates. At 3 months, 33 (49%) of 67 were alive and independent of dialysis after intravenous methylprednisolone, as compared with 48 (69%) of 70 after PE. As compared with intravenous methylprednisolone, PE was associated with a reduction in risk for progression to end-stage renal disease of 24% at 12 months. At 1 year, the patient survival rate was 51 (76%) of 67 in the intravenous methylprednisolone group; 51 (73%) of 70 in the PE group; severe adverse event rates, 32 of 67 (48%) in the intravenous methylprednisolone group; 35 of (50%) 70 in the PE group. PE increased the rate of renal recovery in ANCA-associated systemic vasculitis that presented with renal failure when compared with intravenous methylprednisolone. Patient survival and severe adverse event rates were similar in both groups.

Transplantation

Solid Organ Transplant

Prior to 2006, plasmapheresis in the setting of solid organ transplant was not addressed by this policy. However, plasmapheresis has been extensively used in this setting, both as pretransplant prophylaxis (i.e., desensitization) for highly sensitized patients at high risk of antibody-mediated rejection (AMR), and as a treatment of AMR after transplant. Desensitization protocols vary among transplant centers; two commonly used protocols are referred to as the Cedars-Sinai protocol and the Johns Hopkins protocol. The Cedars-Sinai protocol consists of high-dose IVIg (2 g/kg) and is offered to patients awaiting either a deceased or live donor. The Johns Hopkins protocol consists of low-dose IVIg (100 mg/kg) in combination with plasmapheresis with or without treatment with anti-CD-20 (i.e., Rituxan). Plasmapheresis is more commonly used in patients receiving a living kidney transplant from an ABO mismatched donor. (32) A variety of protocols have also been developed for the treatment of AMR, often in combination with other therapies, such as IVIg or anti-CD-20. e.g. (33-35) The majority of studies of plasmapheresis in the transplant setting are retrospective case series from single institutions. Therefore, it is not possible to compare immunomodulatory regimens to determine their relative efficacy. Nevertheless, in part based on the large volume of literature published on this subject, it appears that plasmapheresis is a component of the standard of care for the management of AMR.

Other Conditions or Applications

Asthma

There has been some research interest in the use of plasmapheresis in patients with severe, steroid-dependent asthma. However, preliminary results do not suggest treatment effectiveness. (36)

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS) and Sydenham's chorea (SC)

PANDAS is defined as rapid, episodic onset of obsessive-compulsive disorder (OCD) and/or tic disorder symptoms after a group A β -hemolytic streptococcal infection (GABHS). SC is the neurologic manifestation of acute rheumatic fever. The choreatic symptoms of Sydenham's chorea are characterized by involuntary rapid and jerky movements that affect the extremities, trunk, and face. SC is generally a self-limited disorder with symptoms resolving in weeks to months. Perlmutter and colleagues conducted an RCT to evaluate the effectiveness of PE and IVIg in reducing the severity of neuropsychiatric symptoms in children diagnosed in the PANDAS subgroup. (37) Children (n=30) with clear evidence of a strep infection as the trigger of their OCD and tics were randomized to receive PE (n=10; 5 to 6 procedures over 2 weeks), IVIg (n=9; 2 gm/kg over 2 days) or placebo (n=10; mimic IVIg). All were severely ill at the time of treatment. At 1 month, both active treatment groups demonstrated symptom improvement, but those in the placebo group were unchanged. The treatment effect was still apparent after 1 year. However, 50% of the children were on the same or higher doses of their baseline medications; thus it is not entirely clear that IVIg or PE had a beneficial effect. This study needs to be replicated with a larger number of patients. The authors noted that children in the placebo group (IVIg control group) subsequently received PE in an open trial and had only minor improvements.

Garvey and colleagues conducted an RCT designed to determine if IVIg or PE would be superior to prednisone in decreasing the severity of chorea. (38) Children with Sydenham's chorea (n=18) were randomized to treatment with PE (n= 8; 5 to 6 procedures over 1 to 2 weeks), IVIg (n=4; 2 gm/kg over 2 days), or prednisone (n=6; 1 mg/kg/day for 10 days followed by taper over next 10 days). The primary outcome was chorea severity at 1 month. The secondary outcome variable was chorea severity at 1 year following treatment. There was no significant difference between the baseline chorea severity scores by the treatment group. Chorea severity was assessed at baseline and at 1, 2, 3, 6, and 12 months following treatment. The chorea rating scale scores range from 0 (no chorea) to 18 (severe or paralytic chorea). A score of 9 or higher was required for study entry. Baseline medications to control choreatic symptoms were discontinued 1 week prior to baseline assessment and each follow-up evaluation. Mean chorea severity for the entire group was lower at the 1-month follow-up evaluation (overall 48% improvement). The between-group differences were not statistically significant. Larger studies are needed to confirm these clinical observations.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

In response to requests, input was received through 2 Physician Specialty Societies and 3 Academic Medical Centers while this policy was under review in 2012. While the various Physician Specialty Societies and Academic Medical Centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the Physician Specialty Societies or Academic Medical Centers, unless otherwise noted. There was consensus or near-consensus that plasma exchange for dense deposit disease with Factor H deficiency and/or elevated C3 nephritis factor, catastrophic antiphospholipid syndrome, focal segmental glomerulosclerosis after renal transplant, and myeloma with acute renal failure may be considered medically necessary. Clinical input was mixed on the medical necessity of hyperviscosity syndromes with renal failure (other than associated with multiple myeloma or Waldenstrom's macroglobulinemia). In addition, there was no consensus about an optimal creatinine threshold for instituting plasma exchange in patients with renal failure associated with ANCA-associated vasculitis or other diagnoses.

Summary

In conclusion, due to data from published studies and/or clinical support, plasma exchange is considered medically necessary for selected conditions. For conditions in which there is a lack of efficacy data and clinical support, plasma exchange is considered investigational.

Practice Guidelines and Position Statements

In 2011, the American Academy of Neurology (Therapeutics and Technology Assessment Subcommittee) issued an evidence-based guideline on plasmapheresis in the treatment of neurological disorders. (39) The primary conclusions based on their evidence review are as follows:

- Established effective
 - Acute inflammatory demyelinating polyneuropathy/ Guillain-Barre syndrome
 - Chronic inflammatory demyelinating polyneuropathy, short-term treatment
- Probably effective
 - Relapses in multiple sclerosis
- Possibly effective
 - Fulminant demyelinating CNS disease
- Established ineffective
 - Chronic or secondary progressive multiple sclerosis
- Insufficient evidence
 - Myasthenia gravis
 - Sydenham's chorea
 - Acute obsessive-compulsive disorder and tics in PANDAS

In 2010, the American Society for Apheresis (ASFA) released updated guidelines on *the use of Therapeutic Apheresis*. (40) The guidelines modified and simplified the categories introduced in 2007; for example, The following is a detailed description of the ASFA categories.

Category	Description
I	Category I includes diseases for which TA [therapeutic apheresis] is accepted as first-line treatment, either as the sole treatment or in conjunction with other treatments. Note that this designation need not imply that TA is mandatory in all cases.
II	Category II denotes diseases for which TA is accepted as second-line treatment, either as the sole treatment or in conjunction with other treatments.
III	Category III diseases are those for which the optimum role of TE is not established and treatment decisions on an individual basis are recommended.
IV	Category IV indicates disorders for which published evidence suggests or demonstrates that TE is ineffective or harmful.

Below are the indications for therapeutic plasma exchange followed by the ASFA category recommendations for 2007 and 2010.

Indication Categories for Therapeutic Apheresis- Plasma Exchange

Disease Group / Name / Condition	AFSA 2007	AFSA 2010
Autoimmune		
Catastrophic antiphospholipid syndrome	III	II
Cryoglobulinemia	I	I
Pemphigus vulgaris	III	IV
Systemic lupus erythematosus		
Manifestations other than nephritis	III	NC
Severe	NC	II
Nephritis	IV	IV

Hematologic		
ABO incompatible hematopoietic progenitor cell transplantation	II	II
Aplastic anemia	III	III
Pure red blood cell aplasia	III	II
Autoimmune hemolytic anemia		
Warm autoimmune hemolytic anemia	III	III
Cold agglutinin disease	III	II
Hyperviscosity in monoclonal gammopathies	I	I
Idiopathic thrombocytopenic purpura		
Refractory immunoadsorption	II	NC
Refractory or non-refractory	IV	NC
Myeloma and acute renal failure (in 2010, myeloma cast nephropathy)	III	II
Post-transfusion purpura	III	III
Red blood cell alloimmunization in pregnancy	II	II
Thrombotic thrombocytopenic purpura	I	I
Metabolic		
Acute liver failure	III	III
Sepsis (in 2010, sepsis with multiorgan failure)	III	III
Thyrotoxicosis (in 2010, thyroid storm)	III	III
Neurological		
Acute disseminated encephalomyelitis	III	II
Acute Inflammatory demyelinating polyneuropathy (Guillain-Barre syndrome)	I	I
Chronic inflammatory demyelinating polyradiculoneuropathy	I	I
Lambert-Eaton myasthenic syndrome	II	II
Multiple Sclerosis		
Acute CNS inflammatory demyelinating disease	II	II
Devic's syndrome	III	NC
Chronic progressive	III	III
Myasthenia gravis	I	I
Paraneoplastic neurologic syndromes	III	III
Paraproteinemic polyneuropathies		
IgG/IgA	I	I
IgM	II	I
Multiple Myeloma	III	III
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; Sydenham's chorea		
Severe PANDAS (2010 exacerbations)	I	I
Severe SC	I	I
Rasmussen's encephalitis	II	NC
Stiff-person syndrome	III	IV
Renal		
ANCA-associated rapidly progressive		
Glomerulonephritis (Wegener's granulomatosis)	II	
Dialysis dependence	NC	III
Dialysis independence	NC	III
Anti-glomerular basement membrane disease		
Goodpasture's syndrome	I	
Diffuse alveolar hemorrhage (DAH)	NC	I
Dialysis dependence and no DAH	NC	IV
Dialysis independence	NC	I
Focal segmental glomerulosclerosis		
Primary	III	NC
Secondary	III	NC
Recurrent	NC	I

Hemolytic uremic syndrome (HUS); thrombotic microangiopathy; transplant-associated microangiopathy		
Idiopathic HUS	III	III
Transplant-associated microangiopathy	III	NC
Diarrhea-associated, pediatric	IV	NC
Atypical HUS due to complement factor gene mutations	NC	II
Atypical HUS due to autoantibody to factor H	NC	I
Diarrhea-associated HUS or typical HUS	NC	IV
Rapidly progressive glomerulonephritis	III	NC
Renal transplantation; antibody mediated rejection; HLA desensitization		
Antibody mediated rejection	II	I
LA desensitization	II	NC
Desensitization, living donor, positive	NC	II
Crossmatch due to donor-specific HLA antibody		
High PRI: cadaveric donor	NC	III
Rheumatic		
Scleroderma (progressive systemic sclerosis)	III	III
Transplantation		
ABO incompatible solid organ transplantation		
Kidney	II	II
Heart (infants)	II	II
Liver (2010 preoperative)	III	III
Heart transplant rejection		
Treatment	III	NC

Abbreviations: NC – not-categorized

Medicare National Coverage

The Centers for Medicare and Medicaid Services, Medicare Coverage Database, National Coverage Determination (NCD) for apheresis (therapeutic pheresis) (41) states: "For purposes of Medicare coverage, apheresis is defined as an autologous procedure, i.e., blood is taken from the patient, processed, and returned to the patient as part of a continuous procedure (as distinguished from the procedure in which a patient donates blood preoperatively and is transfused with the donated blood at a later date). Apheresis is covered for the following indications: Plasma exchange for acquired myasthenia gravis; Leukapheresis in the treatment of leukemia; Plasmapheresis in the treatment of primary macroglobulinemia (Waldenström); Treatment of hyperglobulinemias, including (but not limited to) multiple myelomas, cryoglobulinemia and hyperviscosity syndromes; Plasmapheresis or plasma exchange as a last resort treatment of thrombotic thrombocytopenic purpura (TTP); Plasmapheresis or plasma exchange in the last resort treatment of life threatening rheumatoid vasculitis; Plasma perfusion of charcoal filters for treatment of pruritis of cholestatic liver disease; Plasma exchange in the treatment of Goodpasture's Syndrome; Plasma exchange in the treatment of glomerulonephritis associated with antglomerular basement membrane antibodies and advancing renal failure or pulmonary hemorrhage; Treatment of chronic relapsing polyneuropathy for patients with severe or life threatening symptoms who have failed to respond to conventional therapy; Treatment of life threatening scleroderma and polymyositis when the patient is unresponsive to conventional therapy; Treatment of Guillain-Barre Syndrome; and Treatment of last resort for life threatening systemic lupus erythematosus (SLE) when conventional therapy has failed to prevent clinical deterioration."

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Coding

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Codes	Number	Description
CPT	36514	Therapeutic apheresis; for plasma pheresis

ICD-9 Procedure	99.71	Therapeutic plasmapheresis
ICD-9 Diagnosis	203.0	Multiple myeloma
	273.2	Other paraproteinemias (Cryoglobulinemia)
	273.3	Macroglobulinemia (includes Waldenström's macroglobulinemia and hyperviscosity syndrome NEC)
	282.8	Other specified hereditary hemolytic anemias (includes sclerothymic hyperviscosity syndrome)
	283.11	Non-autoimmune, hemolytic-uremic syndrome
	287.3	Primary thrombocytopenia
	287.30	Primary thrombocytopenia, unspecified
	287.31	Immune thrombocytopenic purpura
	287.32	Evans' syndrome
	287.33	Congenital and hereditary thrombocytopenic purpura
	287.39	Other primary thrombocytopenia
	287.4	Secondary thrombocytopenia
	289.0	Polycythemia, secondary (includes polycythemic hyperviscosity syndrome)
	340	Multiple sclerosis
	356.9	Unspecified hereditary and idiopathic peripheral neuropathy
	357.0	Acute infective polyneuritis (includes Guillain-Barré syndrome)
	357.81	Chronic inflammatory demyelinating polyneuritis
	358.00	Myasthenia gravis without (acute) exacerbation
	358.01	Myasthenia gravis with (acute) exacerbation
	446.21	Goodpasture's syndrome
	446.4	Wegener's granulomatosis
	446.6	Thrombotic microangiopathy
	642.5	Severe pre-eclampsia
ICD-10-CM (effective 10/01/14)	C88.0	Waldenstrom macroglobulinemia (includes macroglobulinemia)
	D58.0 – D58.9	Other hereditary hemolytic anemias code range
	D59.3	Hemolytic-uremic syndrome
	D69.3	Immune thrombocytopenic purpura (includes idiopathic thrombocytopenic purpura)
	D69.49	Other primary thrombocytopenia
	D69.5	Thrombocytopenia, unspecified
	D75.1	Secondary polycythemia
	D89.2	Hypergammaglobulinemia, unspecified
	G35	Multiple sclerosis
	G60.9	Hereditary and idiopathic neuropathy, unspecified
	G61.0	Guillain-Barre syndrome (includes acute infective polyneuritis)
	G61.81	Chronic inflammatory demyelinating polyneuritis
	G70.00 – G70.01	Myasthenia gravis, code range
	M31.0	Hypersensitivity angitis (includes Goodpasture's syndrome)
	M31.30 – M31.31	Wegener's granulomatosis code range
	O14.20 – O14.23	HELLP syndrome code range
ICD-10-PCS (effective 10/01/14)	6A550Z3, 6A551Z3	Plasmapheresis, code single or multiple
HCPCS		
Type of Service	Therapy	
Place of Service	Inpatient / Outpatient	

Appendix

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Diagnostic Criteria for Diagnosis of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

The following criteria are adapted from the Task Force Report of the Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force (*Neurology* 1991; 41:617-18). The report included mandatory, supportive, and exclusionary diagnostic criteria. Only the mandatory criteria are excerpted here. The criteria are based on a combination of clinical observations, physiologic studies, pathologic features (i.e., nerve biopsy), and studies of the cerebral spinal fluid (CSF).

- **Clinical: Mandatory**

- Progressive or relapsing motor and sensory, rarely only motor or sensory, dysfunction of more than 1 limb or a peripheral nerve nature, developing over at least 2 months.
- Hypo- or areflexia. This will usually involve all four limbs.

- **Physiologic Studies: Mandatory.**

Nerve conduction studies including studies of proximal nerve segments in which the predominant process is demyelination.

Must have 3 out of 4 of the following criteria in the list of second-level bullets:

- Reduction in conduction velocity (CV) in 2 or more motor nerves
 - < 80% of lower limit of normal (LLN) is amplitude > 80% of LLN
 - < 70% of LLN is amplitude < 80% of LLN
- Partial conduction block or abnormal temporal dispersion in 1 or more motor nerves: either peroneal nerve between ankle and below fibular head, median nerve between wrist and elbow, or ulnar nerve between wrist and below elbow.
- Criteria suggestive of partial conduction block: < 15% change in duration between proximal and distal sites and > 20% drop in negative-peak (p) area or peak to peak (p-p) amplitude between proximal and distal sites.
- Criteria for abnormal temporal dispersion and possible conduction block: > 15% change in duration between proximal and distal sites and > 20% drop in p area or p-p amplitude between proximal and distal sites and > 20% drop in p or p-p amplitude between proximal and distal sites. These criteria are only suggestive of partial conduction block as they are derived from studies of normal individuals.
- Additional studies, such as stimulation across short segments or recording of individual motor unit potentials, are required for confirmation.
- Prolonged distal latencies in two or more nerves:
 - >125% of upper limit of normal (LEN) is amplitude > 80% of LLN
 - >150% of LEN if amplitude < 80% of LLN
- Absent F waves or prolonged minimum:
 - > 120% of ULN if amplitude > 80% of LLN
 - > 150% of ULN if amplitude < 80% of LLN

- **Pathologic Features: Mandatory**

Nerve biopsy showing unequivocal evidence of demyelination and remyelination.

Demyelination by either electron microscopy (> 5 fibers) or teased fiber studies >12% of 50 fibers, minimum of 4 internodes each, demonstrating demyelination/ remyelination.

- **CSF Studies: Mandatory**

- Cell count <10/mm-3 if HIV-seronegative or <50/mm-3 if HIV seropositive
- Negative VDRL

Guillain-Barré Syndrome Disability Scale

The following is the disability scale as first described by Hughes et al. in Lancet 1978; 2(8093):750-3.

0. Healthy
1. Minor symptoms or signs of neuropathy but capable of manual work
2. Able to walk without support of a stick but incapable of manual work

3. Able to walk with a stick, appliance or support
4. Confined to bed or chair bound
5. Requiring assisted ventilation
6. Dead

The scale has been modified since 1978 and appears below as it did in the Hughes et al. 2007 systematic review published in Brain 2007; 130(9):2245-57.

0. Healthy
1. Minor symptoms or signs of neuropathy but capable of manual work/capable of running
2. Able to walk without support of a stick (*5 m across an open space*) but incapable of manual work/running
3. Able to walk with a stick, appliance or support (5m across an open space)
4. Confined to bed or chair bound
5. Requiring assisted ventilation (for any part of the day or night)
6. Death

History

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Date	Reason
11/13/01	Replace Policy - Revised Policy replaces P8.02.100
08/13/02	Replace Policy - Policy reviewed; new indications added.
05/13/03	Replace Policy - Update CPT codes only.
05/11/04	Replace Policy - Policy reviewed with literature search; references added. No change in policy statement.
06/14/05	Replace Policy - Policy updated with literature search; no change in policy statement. Reference 22 updated, and comparison between ASA recommendations and policy statement included in the Rationale Section.
02/06/06	Codes updated - No other changes.
05/16/06	Update Scope and Disclaimer - No other changes.
08/08/06	Replace Policy - Policy revised with addition of policy statements and discussion of plasmapheresis in the setting of solid organ transplantation, considered medically necessary; references added.
06/09/09	Replace Policy - Policy updated with literature search. Policy statement updated to include Wegener's Granulomatosis as a medically necessary indication.
04/13/10	Replace Policy - Policy reviewed with literature search The policy statement has been modified to include: Guillain-Barré syndrome severity grades 1-2 as medically necessary; use in the pediatric population is investigational for mild and moderate forms of GBS and medically necessary for the severe form of GBS; the policy statement has been modified to include severe manifestations of mixed cryoglobulinemia (MC) as medically necessary when used in combination with immunosuppressive therapy; typical- hemolytic uremic syndrome is investigational (considered medically necessary in previous updates) and investigational for treatment of PANDAS, Sydenham Chorea, Refsum's disease, cryoglobulinemia (except severe MC), myasthenia gravis with anti-MuSk antibodies; additional conditions were added as investigational based on American Society for Apheresis (ASFA) review. Title changed from "Plasma Exchange (Plasmapheresis) to "Plasma Exchange." References added.
06/08/10	Cross Reference Update - No other changes.
06/13/11	Replace Policy - Policy reviewed with literature search from May 2009 through January 2011. No changes to policy statements. Rationale rewritten. References 16, 24, 31 and 41 added; other references renumbered or removed. ICD-10 codes added to policy.
06/20/12	Minor update: Related Policies updated; 8.01.17 replaced 8.01.507 effective June 12, 2012.
07/10/12	Replace policy. Policy statement revised with additional conditions that may be medically necessary myeloma with acute renal failure, catastrophic antiphospholipid syndrome; dense deposit disease with Factor H deficiency and/or elevated C3 nephritis factor and focal segmental glomerulosclerosis after renal transplant. The investigational statement on focal segmental glomerulosclerosis was modified to indicate that it applied to situations other than after renal transplant. Hyperviscosity syndromes with renal failure (other than associated with multiple myeloma or Waldenstrom's macroglobulinemia) added as investigational. In addition, the serum creatinine threshold was removed from the medically necessary policy statement on ANCA-associated vasculitis. Rationale rewritten. Updated literature review with references 22, 26 and 29 added, other references renumbered or removed.
09/28/12	Update Related Policies – Add 7.03.509; ICD-10 codes are now effective 10/01/2014.
02/11/13	Replace policy. Minor clarification regarding medical necessity of MS for acute and chronic forms. The intent of the policy statement is unchanged.
04/18/13	Update Related Policies. Change title to 8.01.36.
07/24/13	Replace policy. Policy reviewed with literature search through March 21, 2013. Policy statements unchanged. References 19, 23 and 40 added.
08/15/13	Update Related Policies. Change title to 7.03.05.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT

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Lp-PLA2 Assay

Question: Should coverage of the Lp-PLA2 assay (PLAC test) be added to the Prioritized List?

Question source: diaDexus

Issue: The PLAC test is an assay for Lipoprotein-associated Phospholipase A2 (Lp-PLA2) (CPT 83698). Currently, this test is on the Never Covered List. The manufacturer, diaDexus, has requested review of coverage for this test.

Lipoprotein-associated phospholipase A2 (Lp-PLA2), also known as platelet-activating factor acetylhydrolase, is an enzyme that hydrolyzes phospholipids and is primarily associated with low-density lipoproteins (LDLs). Accumulating evidence has suggested that Lp-PLA2 is a biomarker of coronary artery disease (CAD) and may have a proinflammatory role in the progression of atherosclerosis.

From diaDexus

The PLAC Test is an FDA-cleared assay for Lp-PLA₂, to be used as an aid in the assessment of risk for coronary and ischemic stroke associated with atherosclerosis. In 2007 the PLAC Test was granted a Category I CPT Code (83698) by the American Medical Association and is reimbursed by the Centers for Medicare and Medicaid Services. The PLAC Test is available nationwide from reference and specialty laboratories (including Quest Diagnostics and Lab Corp). Additional information can be found at www.plactest.com.

No national coverage determination (“NCD”) for the PLAC Test exists with CMS, and all but two Medicare jurisdictions have no ICD-9 limitations for coverage. I recently learned that Medicaid in Oregon currently does not provide coverage for the PLAC Test (one of only 5 state Medicaid plans not providing coverage).

Evidence

1) Emerging Risk Factors Collaboration 2012

- a. Prospective cohort study
- b. N=165, 544 participants without baseline CVD in 37 prospective cohorts (calendar years of recruitment: 1968-2007)
- c. median follow-up of 10.4 years (interquartile range, 7.6-14 years)
- d. Additional testing with...lipoprotein-associated phospholipase A₂ mass would categorize an additional 2.7% of people to a 20% or higher predicted CVD risk category and, therefore, in need of statin treatment under Adult Treatment Panel III guidelines.
- e. **Conclusion** In a study of individuals without known CVD, the addition of information on the combination of apolipoprotein B and A-I, lipoprotein(a), or lipoprotein-associated phospholipase A₂ mass to risk scores containing total cholesterol and HDL-C led to slight improvement in CVD prediction.

Lp-PLA2 Assay

2) **European Guidelines on cardiovascular disease prevention in clinical practice (version 2012)**

- a. LpPLA2 remains a 'second-line' marker for CVD risk estimation.
- b. Recommendation: LpPLA2 may be measured as part of a refined risk assessment in patients at high risk of a recurrent acute atherothrombotic event [level of recommendation IIB, level of evidence B, GRADE: weak]

Other policies

1) **Premara BCBS 2013**

- a. Considers the Lp-PLA2 assay investigational
 - i. There is a large amount of evidence establishing that Lp-PLA2 levels are an independent predictor of cardiovascular risk factors, physiologic measures of cardiac disease, and cardiovascular events. This association has been demonstrated in a variety of clinical populations, in individuals both with and without cardiovascular disease. The evidence on the ability of Lp-PLA2 to reclassify patients into clinically relevant categories is less convincing, with the largest patient-level meta-analysis reporting no significant improvement.

Summary: Lp-PLA2 assay is correlated with cardiovascular disease; however, it does not appear to have a significant clinical utility.

HERC staff recommendation:

- 1) Make no change to the current placement of the Lp-PLA2 assay on the Never Covered List

Lp-PLA2 Assay

Manufacturer provided studies

1) Dohi 2011

- a. Excluded due to size (N=40)

2) Hatoum 2011

- a. Author(s) noted to have conflict of interest
- b. Case control study using Nurses' Health Study data
- c. N=421 cases and 842 controls
- d. After conditioning on the matching factors, Lp-PLA2 activity was significantly associated with myocardial infarction (relative risk [RR] 2.86 for extreme quartiles, 95% CI 1.98-4.12). Upon additional adjustment for lipid, inflammatory, and clinical risk factors, the RR remained statistically significant (RR 1.75, 95% CI 1.09-2.84).
- e. The addition of Lp-PLA2 activity to a multivariable-adjusted model increased the receiver operating characteristic curves from 0.720 to 0.733 and significantly improved the net reclassification improvement index (P = .004).
- f. Conclusions Levels of Lp-PLA2 activity were significantly associated with incident CHD among women. In addition, Lp-PLA2 activity added significantly to CHD risk discrimination.

3) Pasternak 2003

- a. Excluded as did not specifically address Lp-PLA2

4) Massot 2011

- a. N=75 Women, retrospective cohort study
- b. Lp-PLA2 activity was the only independent predictor for new vascular events (hazard ratio 2.89; 95% CI 1.029 to 8.096; p = 0.044) after multivariate analysis (Cox regression).
- c. Conclusions: Lp-PLA2 activity might be a useful tool to identify intracranial large-artery occlusive disease patients at higher risk of suffering new vascular events.

5) AACE 2012

- a. American Association of Clinical Endocrinologists guidelines for management of dyslipidemia and prevention of atherosclerosis
- b. nontraditional risk factors (including lipoprotein-associated phospholipase A2 [Lp-PLA2] should be considered in screening for dyslipidemia
- c. Screening tests recommended for the detection of CVD:
 - i. Assess markers of inflammation in patients where further stratification of risk is necessary. Highly sensitive CRP and Lp-PLA2 provide useful additional information in these instances and appear to be synergistic in predicting risk of CVD and stroke (**Grade B; BEL 1**).
 - ii. Measure Lp-PLA2, which in some studies has demonstrated more specificity than highly sensitive CRP, when it is necessary to further stratify a patient's CVD risk, especially in the presence of systemic highly sensitive CRP elevations (**Grade 2; BEL B**).
 - iii. Lp-PLA2 has been identified as a strong and independent predictor of CVD events and stroke in patients with and without manifest CAD as well as in patients with low LDL-C. Current best evidence indicates that an Lp-PLA2 level less than 200 ng/mL is normal, ≥ 200 and < 223 ng/mL is

Lp-PLA2 Assay

intermediate, and ≥ 223 ng/mL is high. Lp-PLA2 appears to act synergistically with CRP (described above) such that when both are elevated, risk is substantial. However, while CRP is a marker of general inflammation, Lp-PLA2 appears to specifically indicate vascular inflammation and is not influenced by obesity.

6) Davidson 2008

- a. Note: most authors had conflicts of interest
- b. Consensus panel for recommendations on appropriate use of lipoprotein-associated phospholipase A2 (Lp-PLA2)
- c. Lp-PLA2 is recommended as an adjunct to traditional risk assessment in patients at moderate and high 10-year risk.
- d. elevated Lp-PLA2 levels should prompt consideration of increasing the cardiovascular risk category from moderate to high or high to very high risk, respectively.
- e. Because intensification of lifestyle changes and low-density lipoprotein (LDL) cholesterol lowering is beneficial in high-risk patients, regardless of baseline LDL cholesterol levels, consideration should be given to lowering the LDL cholesterol target by 30 mg/dL (1 mg/dL $\approx$ 0.02586 mmol/L) in patients with high levels of Lp-PLA2.
- f. Lp-PLA2 is recommended as a diagnostic test for vascular inflammation to better identify patients at high or very high risk who will benefit from intensification of lipid-modifying therapies.
- g. However, at this time Lp-PLA2 cannot be recommended as a target of therapy.

7) The Lp-PLA2 Studies Collaboration 2010

- a. Analysis of individual records from 79 036 participants in 32 prospective studies
- b. meta-analysis of within-study regressions to calculate risk ratios (RRs) per 1 SD higher value of Lp-PLA2 or other risk factor. lipids.
- c. We noted roughly log-linear associations of Lp-PLA2 activity and mass with risk of coronary heart disease and vascular death. RRs, adjusted for conventional risk factors, were: 1.10 (95% CI 1.05–1.16) with Lp-PLA2 activity and 1.11 (1.07–1.16) with Lp-PLA2 mass for coronary heart disease; 1.08 (0.97–1.20) and 1.14 (1.02–1.27) for ischaemic stroke; 1.16 (1.09–1.24) and 1.13 (1.05–1.22) for vascular mortality; and 1.10 (1.04–1.17) and 1.10 (1.03–1.18) for non-vascular mortality, respectively.
- d. Adjusted RRs for coronary heart disease were 1.10 (1.02–1.18) with non-HDL cholesterol and 1.10 (1.00–1.21) with systolic blood pressure.
- e. Interpretation Lp-PLA2 activity and mass each show continuous associations with risk of coronary heart disease, similar in magnitude to that with non-HDL cholesterol or systolic blood pressure in this population. Associations of
- f. Lp-PLA2 mass and activity are not exclusive to vascular outcomes, and the vascular associations depend at least partly on lipids.

8) Pitt 1999

- a. Excluded as >10 yrs old

9) Tikkanen 2009

- a. Excluded as did not specifically evaluate Lp-PLA2



August 6, 2013

Ariel K. Smits, MD MPH
Medical Director, Health Evidence Review Commission
1225 Ferry St. SE, 1st Floor
Salem, OR 97301

Via email

Dear Dr. Smits:

I'm contacting you on behalf of diaDexus, Inc. which developed and distributes PLAC Test. The PLAC Test is an FDA-cleared assay for Lp-PLA₂, to be used as an aid in the assessment of risk for coronary and ischemic stroke associated with atherosclerosis. In 2007 the PLAC Test was granted a Category I CPT Code (83698) by the American Medical Association and is reimbursed by the Centers for Medicare and Medicaid Services. The PLAC Test is available nationwide from reference and specialty laboratories (including Quest Diagnostics and Lab Corp). Additional information can be found at www.plactest.com.

No national coverage determination ("NCD") for the PLAC Test exists with CMS, and all but two Medicare jurisdictions have no ICD-9 limitations for coverage. Jurisdiction M (Palmetto GBA) recently updated and expanded coverage effective February 14, 2013. Likewise, Jurisdiction H (Novitas Solutions) approved our request to expand coverage in May, 2013. There are no ICD-9 code limitations or Local Coverage Determination for the PLAC Test with Noridian Administrative Services, which as you know, is the Medicare Administrative Contractor for the State of Oregon. We believe that all but 5 state Medicaid programs (including Oregon) provide coverage for the PLAC Test (an Excel file for all 50 states is included to demonstrate where coverage exists). We are requesting that the PLAC test is recognized and covered by Oregon Medicaid.

Assessment of "Intermediate Risk" for Cardiovascular Disease Tests

Despite gradual declines in incident coronary heart disease (CHD) over the last thirty years, cardiovascular disease remains the major cause of death in the general population. There are surgical and medical interventions for symptomatic CHD; however, the first line of intervention is behavioral risk management, which can have a substantial impact on CHD risk in both primary and secondary prevention.

Stratification of cardiovascular risk is based on traditional risk factors (age, gender, tobacco history) and biomarkers including blood pressure and cholesterol levels. However the majority of cardiac morbidity is in patients who are not identified beforehand as having high risk.¹ Of those patients who are risk stratified with the tradition risk assessment tools, the majority are classified as "intermediate" risk (the NCEP-ATP III Guidelines recommend risk stratification with the Framingham Risk Score, which categorizes low risk at <10% ten-year risk; intermediate risk at 10-20% over 10 years and high risk, in which the ten year risk of coronary heart disease exceeds 20%). Most CHD events occur in those patients who are categorized as having intermediate risk. The

¹ Pasternak RC et al. (2003) Task Force #1, Identification of coronary heart disease risk: is there a detection gap? J Amer Coll Cardiol 41:1863.

misclassification of risk within the current risk stratification scheme is recognized by many clinicians, who are interested in additional tools to improve patient assessment and management.

Coverage for Intermediate-Risk Measurement of Lp-PLA₂ is Reasonable

Innumerable independent studies confirm the incremental value of Lp-PLA₂ as a marker cardiovascular risk. Lp-PLA₂ has been validated as an independent risk marker, with incremental risk prediction which is equivalent to hypertension and HDL cholesterol².

Lp-PLA₂ has been incorporated into several recent clinical guidelines, including those issued by the American Association of Clinical Endocrinologists (AACE). It is recognized as having clinical utility in intermediate risk patients, when further risk stratification is desired.³ Specifically, "...Lp-PLA₂ provide(s) useful additional information in these instances and appear to be synergistic (with hs-CRP) in predicting risk of CVD and stroke." Additionally, the guidelines state, "...while CRP is a marker of general inflammation, Lp-PLA₂ appears to specifically indicate vascular inflammation and is not influenced by obesity" and "Measurement of Lp-PLA₂...may be helpful when it is necessary to further stratify a patient's risk for CVD, especially in the presence of systemic CRP elevations." This endorsement by a major clinical guidelines committee outlines a strategy for more precise risk stratification, which is the basis for therapies. The AACE guidelines confirm that Lp-PLA₂ is specific for vascular inflammation and affords additional information over biomarkers of general inflammation (such as hs-CRP). A copy of the 2012 AACE guidelines is provided as a supplement to this request letter.

Consensus reviews and meta-analyses

In a major consensus review published in 2008 in the *American Journal of Cardiology*, Lp-PLA₂ was recommended as an adjunct to traditional risk assessment in patients with intermediate 10-year risk, "to better identify patients at high or very high risk" who benefit from intensification of therapeutic interventions.⁴

In an independent international review published in *The Lancet* in 2010, the incremental risk carried by elevated Lp-PLA₂ was found to be equivalent to that associated with elevated cholesterol or elevated blood pressure⁵.

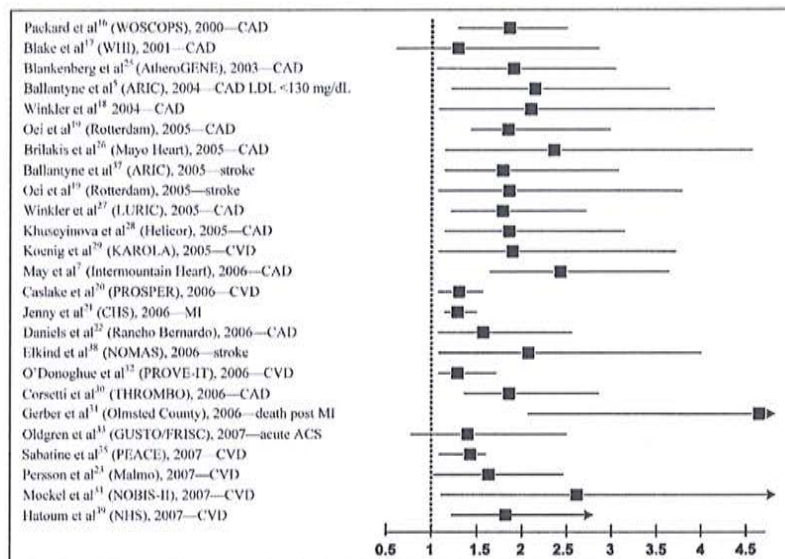
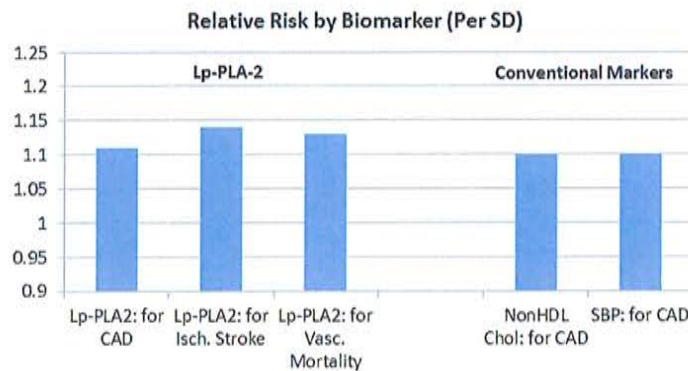
² Lp-PLA₂ Studies Collaboration (2010) Lipoprotein-associated phospholipase A2 and risk of coronary artery disease, stroke, and mortality: collaborative analysis of 32 prospective studies. *Lancet* 375:1536-1544.

³ Jellinger et al. (2012) American Association of Clinical Endocrinologists' guidelines for the management of dyslipidemia and prevention of atherosclerosis. *Endocrine Practice* 18(S1):1-78.

⁴ Davidson MH et al. (2008) Consensus panel recommendation for incorporating lipoprotein-associated phospholipase A2 testing into cardiovascular disease risk assessment guidelines. *Am J Cardiol* 101S:51-57.

⁵ Lp-PLA₂ Studies Collaboration (2010) Lipoprotein-associated phospholipase A2 and risk of coronary artery disease, stroke, and mortality: collaborative analysis of 32 prospective studies. *Lancet* 375:1536-1544.

Relative Risks of Lp-PLA2 elevation per SD, after adjustment for conventional risk factors Lancet meta-analysis (2010)



The relative risk associated with elevated Lp-PLA₂ levels has been reported in the range of 1.1/standard deviation of Lp-PLA₂ elevation in a meta-analysis of over 79,000 patients (Lancet), with individual studies reporting a risk ratio of up to 2.0 (delineating a 100% increase in the risk of CVD events in those individuals with elevated levels of Lp-PLA₂). In addition to the Lancet meta-there are additional independent studies in special populations:

- Hatoum IJ et al. (2011) Lipoprotein associated phospholipase A2 activity improves risk discrimination of incident coronary heart disease among women. *Am Heart J* 161:516-22.
- Massott A et al. (2011) Lipoprotein-associated phospholipase A2 testing usefulness among patients with symptomatic intracranial atherosclerotic disease. *Atherosclerosis* 218:181-7.
- Dohi T et al. (2011) Decreased circulating lipoprotein-associated phospholipase A2 levels are associated with coronary plaque regression in patients with acute coronary syndrome. *Atherosclerosis* 219:907-12.

Lp-PLA₂ Can Drive Actionable Decisions in Intermediate-Risk Patients

Physicians have a range of interventions and recommendations to manage the risk of both primary and secondary cardiovascular disease, including more aggressive lipid control, more aggressive control of diabetes and hypertension, and more assertive endorsement of behavioral health modifications and interventions. In addition, better identification of risk can substantially impact patient compliance in patients at cardiovascular risk.⁶ In high-risk populations the utility of more aggressive management of lipid profiles has been validated with extensive trials evidence.^{7,8}

Thank you in advance for your consideration. Please do not hesitate to contact me at 650 246-6428 if you have questions or would like to discuss our request.

Sincerely,

Robert J. Schott, MD, MPH, FACC
Vice President, Medical Affairs

APPENDIX:

Papers cited in footnotes in this Letter

⁶ For example, calcium scoring reports significantly increase patient compliance with statins: Orakzai (2008) Am J Cardiol 101:999; Schartz J (2011) J Behav Med 34:148.

⁷ Pitt B et al. (1999) Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. New Engl J Med 341:70-76;

⁸ Tikkanen MJ et al. (2009) Total cardiovascular disease burden: comparing intensive with moderate statin therapy insights from the IDEAL trial. J Am Coll Cardiol 54:2353-7.



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Audio Interview

Lipid-Related Markers and Cardiovascular Disease Prediction

The Emerging Risk Factors
Collaboration*

ROUTINELY USED RISK PREDICTION scores for cardiovascular disease (CVD) contain information on total cholesterol and high-density lipoprotein cholesterol (HDL-C) and several other conventional risk factors.^{1,2} There is considerable interest in whether CVD prediction can be improved by assessment of various additional lipid-related markers either to replace, or supplement, traditional cholesterol measurements in these scores.³

Proposals to replace information on total cholesterol and HDL-C with single parameters, such as the total cholesterol:HDL-C ratio or non-HDL-C (ie, total cholesterol – HDL-C),^{4,5} have been motivated by a desire for greater simplicity and a belief that these parameters better reflect the underlying atherosclerotic process. For example, non-HDL-C reflects the cholesterol content of several proatherogenic lipoprotein subfractions (very low-density lipoprotein, intermediate-density lipoprotein, and chylomicron remnants) in addition to low-density lipoprotein cholesterol.

Similar considerations apply to proposals to replace information on total cholesterol and HDL-C with apolipoprotein B and apolipoprotein A-I.⁶⁻⁹ Because apolipoprotein B and A-I are the principal surface proteins found on proatherogenic lipoproteins and HDL, respectively, they might be more strongly

Context The value of assessing various emerging lipid-related markers for prediction of first cardiovascular events is debated.

Objective To determine whether adding information on apolipoprotein B and apolipoprotein A-I, lipoprotein(a), or lipoprotein-associated phospholipase A₂ to total cholesterol and high-density lipoprotein cholesterol (HDL-C) improves cardiovascular disease (CVD) risk prediction.

Design, Setting, and Participants Individual records were available for 165 544 participants without baseline CVD in 37 prospective cohorts (calendar years of recruitment: 1968-2007) with up to 15 126 incident fatal or nonfatal CVD outcomes (10 132 CHD and 4994 stroke outcomes) during a median follow-up of 10.4 years (interquartile range, 7.6-14 years).

Main Outcome Measures Discrimination of CVD outcomes and reclassification of participants across predicted 10-year risk categories of low (<10%), intermediate (10%–<20%), and high (≥20%) risk.

Results The addition of information on various lipid-related markers to total cholesterol, HDL-C, and other conventional risk factors yielded improvement in the model's discrimination: C-index change, 0.0006 (95% CI, 0.0002-0.0009) for the combination of apolipoprotein B and A-I; 0.0016 (95% CI, 0.0009-0.0023) for lipoprotein(a); and 0.0018 (95% CI, 0.0010-0.0026) for lipoprotein-associated phospholipase A₂ mass. Net reclassification improvements were less than 1% with the addition of each of these markers to risk scores containing conventional risk factors. We estimated that for 100 000 adults aged 40 years or older, 15 436 would be initially classified at intermediate risk using conventional risk factors alone. Additional testing with a combination of apolipoprotein B and A-I would reclassify 1.1%; lipoprotein(a), 4.1%; and lipoprotein-associated phospholipase A₂ mass, 2.7% of people to a 20% or higher predicted CVD risk category and, therefore, in need of statin treatment under Adult Treatment Panel III guidelines.

Conclusion In a study of individuals without known CVD, the addition of information on the combination of apolipoprotein B and A-I, lipoprotein(a), or lipoprotein-associated phospholipase A₂ mass to risk scores containing total cholesterol and HDL-C led to slight improvement in CVD prediction.

JAMA. 2012;307(23):2499-2506

www.jama.com

related to CVD risk than is the cholesterol contained in these lipoproteins. However, perhaps partly due to inconclusive epidemiological evidence, there are conflicting guidelines about the relevance of apolipoprotein B and A-I to CVD prediction.^{1,6-11}

There is also debate about the value of supplementing conventional risk factors with targeted assessment of lipoprotein(a). In 2010, the European Atherosclerosis Society Consensus Panel

recommended lipoprotein(a) measurement to augment risk assessment in people at intermediate (10%–<20%) or high (≥20%) predicted 10-year CVD risk.¹² However, the 2010 American College of Cardiology Foundation/American Heart Association Task Force

*Authors/Members Writing Committee and Investigators are listed at the end of this article.

Corresponding Author: John Danesh, FRCP, Department of Public Health and Primary Care, University of Cambridge, Worts Causeway, Cambridge, CB1 8RN, England (erfc@phpc.cam.ac.uk).

For editorial comment see p 2540.

Author Audio Interview available at
www.jama.com.

European Guidelines on cardiovascular disease prevention in clinical practice (version 2012)

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**The Fifth Joint Task Force of the European Society
of Cardiology and Other Societies on Cardiovascular Disease
Prevention in Clinical Practice (constituted by representatives
of nine societies and by invited experts)**

**Developed with the special contribution of the European Association for
Cardiovascular Prevention & Rehabilitation (EACPR)[†]**

Authors/Task Force Members: Joep Perk (Chairperson) (Sweden)^{*}, Guy De Backer¹ (Belgium), Helmut Gohlke¹ (Germany), Ian Graham¹ (Ireland), Željko Reiner² (Croatia), WM Monique Verschuren¹ (The Netherlands), Christian Albus³ (Germany), Pascale Benlian¹ (France), Gudrun Boysen⁴ (Denmark), Renata Cifkova⁵ (Czech Republic), Christi Deaton¹ (UK), Shah Ebrahim¹ (UK), Miles Fisher⁶ (UK), Giuseppe Germano¹ (Italy), Richard Hobbs^{1,7} (UK), Arno Hoes⁷ (The Netherlands), Sehnaz Karadeniz⁸ (Turkey), Alessandro Mezzani¹ (Italy), Eva Prescott¹ (Denmark), Lars Ryden¹ (Sweden), Martin Scherer⁷ (Germany), Mikko Syväne⁹ (Finland), Wilma JM Scholte Op Reimer¹ (The Netherlands), Christiaan Vrints¹ (Belgium), David Wood¹ (UK), Jose Luis Zamorano¹ (Spain), Faiez Zannad¹ (France).

Other experts who contributed to parts of the guidelines: Marie Therese Cooney (Ireland).

ESC Committee for Practice Guidelines (CPG): Jeroen Bax (Chairman) (The Netherlands), Helmut Baumgartner (Germany), Claudio Ceconi (Italy), Veronica Dean (France), Christi Deaton (UK), Robert Fagard (Belgium), Christian Funck-Brentano (France), David Hasdai (Israel), Arno Hoes (The Netherlands), Paulus Kirchhof (Germany), Juhani Knuuti (Finland), Philippe Kolh (Belgium), Theresa McDonagh (UK), Cyril Moulin

^{*}Corresponding author: Joep Perk, School of Health and Caring Sciences, Linnaeus University, Stagneliusgatan 14, SE-391 82 Kalmar, Sweden. Tel: +46 70 3445096, Fax: +46 491 782 643 Email: joep.perk@lnu.se

[†]Other ESC entities having participated in the development of this document:

Associations: European Association of Echocardiography (EAE), European Association of Percutaneous Cardiovascular Interventions (EAPCI), European Heart Rhythm Association (EHRA), Heart Failure Association (HFA)

Working Groups: Acute Cardiac Care, e-Cardiology, Cardiovascular Pharmacology and Drug Therapy, Hypertension and the Heart

Councils: Basic Cardiovascular Science, Cardiology Practice, Cardiovascular Imaging, Cardiovascular Nursing and Allied Professions, Cardiovascular Primary Care

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The disclosure forms of the authors and reviewers are available on the ESC website www.escardio.org/guidelines

(France), Bogdan A. Popescu (Romania), Željko Reiner (Croatia), Udo Sechtem (Germany), Per Anton Sirnes (Norway), Michal Tendera (Poland), Adam Torbicki (Poland), Alec Vahanian (France), Stephan Windecker (Switzerland).

Document Reviewers: Christian Funck-Brentano (CPG Review Coordinator) (France), Per Anton Sirnes (CPG Review Coordinator) (Norway), Victor Aboyans (France), Eduardo Alegria Ezquerra (Spain), Colin Baigent (UK), Carlos Brotons (Spain), Gunilla Burell (Sweden), Antonio Ceriello (Spain), Johan De Sutter (Belgium), Jaap Deckers (The Netherlands), Stefano Del Prato (Italy), Hans-Christoph Diener (Germany), Donna Fitzsimons (UK), Zlatko Fras (Slovenia), Rainer Hambrecht (Germany), Piotr Jankowski (Poland), Ulrich Keil (Germany), Mike Kirby (UK), Mogens Lytken Larsen (Denmark), Giuseppe Mancina (Italy), Athanasios J. Manolis (Greece), John McMurray (UK), Andrzej Pająk (Poland), Alexander Parkhomenko (Ukraine), Loukianos Rallidis (Greece), Fausto Rigo (Italy), Evangelista Rocha (Portugal), Luis Miguel Ruilope (Spain), Enno van der Velde (The Netherlands), Diego Vanuzzo (Italy), Margus Viigimaa (Estonia), Massimo Volpe (Italy), Olov Wiklund (Sweden), Christian Wolpert (Germany).

The disclosure forms of the authors and reviewers are available on the ESC website www.escardio.org/guidelines

Societies: ¹European Society of Cardiology (ESC); ²European Atherosclerosis Society (EAS); ³International Society of Behavioural Medicine (ISBM); ⁴European Stroke Organisation (ESO); ⁵European Society of Hypertension (ESH); ⁶European Association for the Study of Diabetes (EASD); ⁷European Society of General Practice/Family Medicine (ESGP/ FM/WONCA); ⁸International Diabetes Federation Europe (IDF-Europe); ⁹European Heart Network (EHN).

Keywords

Cardiovascular disease, prevention, risk assessment, risk management, smoking, nutrition, physical activity, psychosocial factors

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	with Recent Transient Ischaemic Attack or Ischaemic Stroke
MDRD	Modification of Diet in Renal Disease
MET	metabolic equivalent
MONICA	Multinational MONItoring of trends and determinants in CARdiovascular disease
NICE	National Institute of Health and Clinical Excellence
NRT	nicotine replacement therapy
NSTEMI	non-ST elevation myocardial infarction
ONTARGET	Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial
OSA	obstructive sleep apnoea
PAD	peripheral artery disease
PCI	percutaneous coronary intervention
PROactive	Prospective Pioglitazone Clinical Trial in Macrovascular Events
PWV	pulse wave velocity
QOF	Quality and Outcomes Framework
RCT	randomized clinical trial
RR	relative risk
SBP	systolic blood pressure
SCORE	Systematic Coronary Risk Evaluation Project
SEARCH	Study of the Effectiveness of Additional Reductions in Cholesterol and
SHEP	Systolic Hypertension in the Elderly Program
STEMI	ST-elevation myocardial infarction
SU.FOL.OM3	SUpplementation with FOlate, vitamin B6 and B12 and/or OMega-3 fatty acids
Syst-Eur	Systolic Hypertension in Europe
TNT	Treating to New Targets
UKPDS	United Kingdom Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial
VALUE	Valsartan Antihypertensive Long-term Use
VITATOPS	VITamins TO Prevent Stroke
VLDL	very low-density lipoprotein
WHO	World Health Organization

I. What is cardiovascular disease prevention?

1.1 Introduction

Atherosclerotic cardiovascular disease (CVD) is a chronic disorder developing insidiously throughout life and usually progressing to an advanced stage by the time

symptoms occur. It remains the major cause of premature death in Europe, even though CVD mortality has fallen considerably over recent decades in many European countries. It is estimated that > 80% of all CVD mortality now occurs in developing countries.

CVD causes mass disability: within the coming decades the disability-adjusted life years (DALYs) estimate is expected to rise from a loss of 85 million DALYs in 1990 to a loss of ~150 million DALYs globally in 2020, thereby remaining the leading somatic cause of loss of productivity.¹

CVD is strongly connected to lifestyle, especially the use of tobacco, unhealthy diet habits, physical inactivity, and psychosocial stress.² The World Health Organization (WHO) has stated that over three-quarters of all CVD mortality may be prevented with adequate changes in lifestyle. CVD prevention, remaining a major challenge for the general population, politicians, and healthcare workers alike, is defined as a co-ordinated set of actions, at public and individual level, aimed at eradicating, eliminating, or minimizing the impact of CVDs and their related disability. The bases of prevention are rooted in cardiovascular epidemiology and evidence-based medicine.³

The aim of the 2012 guidelines from the Fifth Joint Task Force (JTF) of the European Societies on Cardiovascular Disease Prevention in Clinical Practice is to give an update of the present knowledge in preventive cardiology for physicians and other health workers. The document differs from 2007 guidelines in several ways: there is a greater focus on new scientific knowledge. The use of grading systems [European Society of Cardiology (ESC) and Grading of Recommendations Assessment, Development, and Evaluation (GRADE)] allows more evidence-based recommendations to be adapted to the needs of clinical practice.

The reader will find answers to the key questions of CVD prevention in the five sections: what is CVD prevention, why is it needed, who should benefit from it, how can CVD prevention be applied, and when is the right moment to act, and finally where prevention programmes should be provided.

A literature search of clinical guidelines aimed at cardiovascular risk assessment in clinical practice identified > 1900 publications.⁴ When these were evaluated using the Appraisal of Guidelines Research and Evaluation (AGREE) instrument, only seven achieved the level considered 'considerable rigour'. Too much guidance and too little impact? The gap between state-of-the-art knowledge and its implementation in clinical practice remains wide, as shown in recent surveys such as EUROASPIRE III.⁵ Family doctors may be flooded with recommendations in the wide field of family medicine. Finding time to read and implement the many guidelines can be an overwhelming task in a busy primary care centre or a regional hospital clinic.

The Task Force behind the 2012 recommendations has chosen to limit the size to the level of the executive summary of previous JTF publications. All relevant reference material is available on the dedicated CVD Prevention Guidelines

✦ Lipoprotein-associated phospholipase A₂ and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies

The Lp-PLA₂ Studies Collaboration*

Summary

Background Lipoprotein-associated phospholipase A₂ (Lp-PLA₂), an inflammatory enzyme expressed in atherosclerotic plaques, is a therapeutic target being assessed in trials of vascular disease prevention. We investigated associations of circulating Lp-PLA₂ mass and activity with risk of coronary heart disease, stroke, and mortality under different circumstances.

Methods With use of individual records from 79 036 participants in 32 prospective studies (yielding 17 722 incident fatal or non-fatal outcomes during 474 976 person-years at risk), we did a meta-analysis of within-study regressions to calculate risk ratios (RRs) per 1 SD higher value of Lp-PLA₂ or other risk factor. The primary outcome was coronary heart disease.

Findings Lp-PLA₂ activity and mass were associated with each other ($r=0.51$, 95% CI 0.47–0.56) and proatherogenic lipids. We noted roughly log-linear associations of Lp-PLA₂ activity and mass with risk of coronary heart disease and vascular death. RRs, adjusted for conventional risk factors, were: 1.10 (95% CI 1.05–1.16) with Lp-PLA₂ activity and 1.11 (1.07–1.16) with Lp-PLA₂ mass for coronary heart disease; 1.08 (0.97–1.20) and 1.14 (1.02–1.27) for ischaemic stroke; 1.16 (1.09–1.24) and 1.13 (1.05–1.22) for vascular mortality; and 1.10 (1.04–1.17) and 1.10 (1.03–1.18) for non-vascular mortality, respectively. RRs with Lp-PLA₂ did not differ significantly in people with and without initial stable vascular disease, apart from for vascular death with Lp-PLA₂ mass. Adjusted RRs for coronary heart disease were 1.10 (1.02–1.18) with non-HDL cholesterol and 1.10 (1.00–1.21) with systolic blood pressure.

Interpretation Lp-PLA₂ activity and mass each show continuous associations with risk of coronary heart disease, similar in magnitude to that with non-HDL cholesterol or systolic blood pressure in this population. Associations of Lp-PLA₂ mass and activity are not exclusive to vascular outcomes, and the vascular associations depend at least partly on lipids.

Funding UK Medical Research Council, GlaxoSmithKline, and British Heart Foundation.

Introduction

Lipoprotein-associated phospholipase A₂ (Lp-PLA₂), an enzyme expressed by inflammatory cells in atherosclerotic plaques,^{1,2} is carried in the circulation bound predominantly to LDL.³ Lp-PLA₂ and other human A₂ phospholipases (such as secretory phospholipase A₂)⁴ propagate inflammation by producing precursors of arachidonic acid from membrane glycerophospholipids.⁵ Lp-PLA₂ (also called platelet-activating factor acetylhydrolase) hydrolyses oxidised phospholipids to yield pro-inflammatory products that are implicated in endothelial dysfunction, plaque inflammation, and formation of necrotic core in plaque,^{6,7} and is postulated to link oxidative modification of LDL and development of inflammatory responses in the arterial intima.^{8,9}

Since the initial report in 2000,¹⁰ many prospective epidemiological studies have investigated the associations between circulating Lp-PLA₂ (assayed either as its enzymatic activity or mass concentration) and subsequent risk of vascular disease outcomes. A meta-analysis of 14 such studies has been reported.¹¹ However, because that review was based on published data, it was unable to

provide detailed analyses (eg, separate examination of associations with coronary heart disease and stroke; characterisation of the shape of any dose-response relations) or to adjust consistently for potential confounding factors.

The objective of the Lp-PLA₂ Studies Collaboration,¹² an analysis of individual data from relevant prospective studies, was to assess the independence, specificity, magnitude, and shape of associations of Lp-PLA₂ with coronary heart disease, stroke, and mortality under different circumstances.

Methods

Study design

Details of study selection and data collection have been described previously.¹² Information about Lp-PLA₂ in relation to major vascular disease morbidity or cause-specific mortality was supplied by 32 prospective studies, 19 of which agreed to participate before their publication. Data were available for 79 036 participants (webappendix pp 2 and 17–20); only two relevant studies (comprising <5% of known incident vascular outcomes) were unable

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*Members listed at end of paper

Correspondence to:

Lp-PLA₂ Studies Collaboration
Coordinating Centre,
Department of Public Health and
Primary Care, University of
Cambridge, Strangeways
Research Laboratory, Cambridge
CB1 8RN, UK
lsc@phpc.cam.ac.uk

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**MEDICAL POLICY**

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Measurement of Lipoprotein-Associated Phospholipase A2 (Lp-PLA2) in the Assessment of Cardiovascular Risk

Number 2.04.32

Effective Date August 16, 2013

Revision Date(s) 08/12/13; 08/14/12; 08/09/11; 08/10/10; 04/13/10; 01/08/08; 02/13/07; 06/16/06; 03/08/05; 01/13/04

Replaces N/A

Policy

Measurement of lipoprotein-associated phospholipase A2 (Lp-PLA2) is considered **investigational**.

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Related Policies

[6.01.56 Myocardial Sympathetic Innervation Imaging in Patients with Heart Failure](#)
[12.04.70 Genetic Testing for Lipoprotein\(a\) Variant\(s\) as a Decision Aid for Aspirin Treatment](#)
[12.04.71 Genotyping for 9p21 Single Nucleotide Polymorphisms to Predict Risk of Cardiovascular Disease or Aneurysm](#)

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Policy Guidelines

Effective January 1, 2007, there is a specific CPT code for this test:

83698: Lipoprotein-associated Phospholipase A2 (Lp-PLA2).

Prior to 2007, there was no specific CPT code for this test. CPT code 83516 (immunoassay, analyte, quantitative, not otherwise specified) might have been used.

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Description

Lipoprotein-associated phospholipase A2 (Lp-PLA2), also known as platelet-activating factor acetylhydrolase, is an enzyme that hydrolyzes phospholipids and is primarily associated with low-density lipoproteins (LDLs). Accumulating evidence has suggested that Lp-PLA2 is a biomarker of coronary artery disease (CAD) and may have a proinflammatory role in the progression of atherosclerosis.

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Background

Low-density lipoproteins (LDL) have been identified as the major atherogenic lipoproteins and have long been identified by the National Cholesterol Education Project (NCEP) as the primary target of cholesterol-lowering therapy. LDL particles consist of a surface coat composed of phospholipids, free cholesterol, and apolipoproteins, surrounding an inner lipid core composed of cholesterol ester and triglycerides. Traditional lipid risk factors such as low-density lipoprotein-cholesterol (LDL-C), while predictive on a population basis, are weaker markers of risk on an individual basis. Only a minority of subjects with elevated LDL and cholesterol levels will develop clinical disease, and up to 50% of cases of coronary artery disease (CAD) occur in subjects with 'normal' levels of total and LDL cholesterol. Thus, there is considerable potential to improve the accuracy of current cardiovascular risk prediction models.

Lipoprotein-associated phospholipase A2 (Lp-PLA2), also known as platelet-activating factor acetylhydrolase, is an enzyme that hydrolyzes phospholipids and is primarily associated with LDLs. Accumulating evidence has suggested that Lp-PLA2 is a biomarker of CAD and may have a proinflammatory role in the progression of atherosclerosis. The recognition that atherosclerosis represents, in part, an inflammatory process has created considerable interest in measurement of proinflammatory factors as part of cardiovascular disease risk assessment.

Regulatory Status

The U.S. Food and Drug Administration (FDA) cleared for marketing an enzyme-linked immunosorbent assay (ELISA) test, the PLAC test (diaDexus, San Francisco, CA), to measure levels of Lp-PLA2.

Scope

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Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply.

Benefit Application

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N/A

Rationale

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This policy was created in October 2003 and updated periodically with literature review. The most recent update with literature review covers the period of April 2012 through May 15, 2013.

A large body of literature has accumulated on the utility of risk factors in the prediction of future cardiac events. The evidence reviewed for this policy statement consists of large, prospective cohort studies that have evaluated the association of lipoprotein-associated phospholipase A2 (Lp-PLA2) with cardiovascular outcomes. A smaller amount of literature is available on the utility of Lp-PLA2 as a treatment target.

The National Cholesterol Education Program (NCEP) ATP-III guidelines (1) document notes that to determine their clinical significance, the emerging risk factors should be evaluated against the following criteria in order to determine their clinical significance:

- Significant predictive power that is independent of other major risk factors
- A relatively high prevalence in the population (justifying routine measurement in risk assessment)
- Laboratory or clinical measurement must be widely available, well standardized, inexpensive, have accepted population reference values, and be relatively stable biologically.
- Preferable, but not necessarily, modification of the risk factor in clinical trials will have shown reduction in risk.

A 2002 TEC Assessment (2) summarized the steps necessary to determine utility of a novel cardiac risk factor. Three steps were required:

- Standardization of the measurement of the risk factor
- Determination of its contribution to risk assessment. As a risk factor, it is important to determine whether the novel risk factor [...] independently contributes to risk assessment compared to established risk factors.
- Determination of how the novel risk assessment will be used in the management of the patient, compared to standard methods of assessing risk, and whether any subsequent changes in patient management result in an improvement in patient outcome.

Lp-PLA2 as a Predictor of Cardiovascular Disease

Results of numerous, large-scale observational studies have examined whether lipoprotein-associated phospholipase A2 (Lp-PLA2) is an independent risk factor for coronary heart disease. A representative sample of some of the larger studies is given below.

The Emerging Risk Factors Collaboration performed a patient-level meta-analysis of the association of novel lipid risk factors with cardiovascular risk. (3) Records from 37 prospective cohort studies enrolling 165,544 participants were combined to predict cardiovascular risk over a median follow-up of 10.4 years. The authors examined the independent association of markers with cardiovascular risk and the ability to reclassify risk into clinically relevant categories. For Lp-PLA2, there were 11 studies enrolling 32,075 participants that measured this factor. Overall, Lp-PLA2 was an independent risk factor for cardiovascular events with a hazard ratio of 1.12 (95% confidence interval [CI]: 1.09-1.21) for each 1 standard deviation (SD) increase in Lp-PLA2 activity. There was no significant improvement in risk reclassification following the addition of Lp-PLA2 to the reclassification model, with a net reclassification improvement of 0.21 (-0.45 to 0.86). The net reclassification improvement crossing 0.0 indicates that the addition of Lp-PLA2 to the model may result in either improvement or worsening of reclassification.

The West of Scotland Coronary Prevention Study (WOSCOPS) was a five-year, case control trial evaluating 6,595 men with elevated cholesterol levels and no history of a heart attack. (4) Researchers looked at a smaller population of this study to determine if inflammatory markers such as Lp-PLA2 and high-sensitivity C-reactive protein (hsCRP) were correlated with coronary heart disease (CHD) events. The 580 men who went on to have a myocardial infarction (MI) or revascularization were compared to 1,160 age- and smoking-matched men who did not have an event. The results showed that those with the highest levels of Lp-PLA2 had twice the risk

of an event compared to those with the lowest levels, even after adjustment for traditional risk factors and other inflammatory mediators.

The Atherosclerosis Risk in Communities (ARIC) study (5) evaluated the various risk markers and their association with increased risk in a large, diverse population of more than 12,000 individuals. At enrollment in the study, patients were free of CHD and were followed up for the development of the disease for the next 9 years. The case-cohort component of the study examined 2 inflammatory markers, Lp-PLA2 and hsCRP, in a subset of 608 cases and 740 controls. The results showed that elevated levels of Lp-PLA2 are higher in incident coronary heart disease cases. In individuals with nonelevated low-density lipoprotein (LDL) levels (less than 130 mg/dL), Lp-PLA2 levels were independently associated with CHD, even after adjustment for traditional risk factors and C-reactive protein. Koenig and colleagues (6) reported similar results in a study of 934 apparently healthy men aged 45 to 64 who were followed up between 1984 and 1998. During this period, 97 men experienced a coronary event. Elevated levels of Lp-PLA2 appeared to be predictive of future coronary events in middle-aged men with moderately elevated total cholesterol, independent of C-reactive protein.

Ballantyne and colleagues (7) studied Lp-PLA2 in the 12,762 apparently healthy individuals participating in the ARIC study. Mean levels of both Lp-PLA2 and C-reactive protein were higher in the 194 stroke cases; the authors concluded that Lp-PLA2 levels may provide complementary information beyond traditional risk factors in identifying those at risk for ischemic stroke. As part of the PEACE study, (8) Lp-PLA2 levels were measured in 3,766 patients with stable CAD followed up for a median of 4.8 years. After adjustment for other baseline risk factors, patients in the highest quartile of Lp-PLA2 were 1.4 times more likely (95% confidence interval [CI]: 1.17–1.70, $p < 0.001$) to experience an adverse cardiovascular outcome compared to patients in the lowest quartile. Winkler and colleagues (9) studied 3,232 consecutive patients referred for coronary angiography and reported that Lp-PLA2 levels were an independent predictor of cardiac mortality (hazard ratio: 2.0; 95% CI: 1.4–3.1, $p < 0.001$) after adjusting for established risk factors, including C-reactive protein and N-terminal b-natriuretic peptide. Persson and colleagues (10) evaluated the relationship between Lp-PLA2 and the metabolic syndrome in 4,480 nondiabetic patients without a history of coronary artery disease (CAD). Both Lp-PLA2 (relative risk [RR]: 1.54; 95% CI: 1.07–2.24) and the metabolic syndrome (RR: 1.42; 95% CI: 1.06–1.90) were significant predictors of a first cardiac event. The combination of both elevated Lp-PLA2 and metabolic syndrome conferred a further increase in risk (RR: 1.97; 95% CI: 1.34–2.90).

The Rancho Bernardo Study (11) enrolled 1,077 community-dwelling elderly individuals without known heart disease and followed up patients a mean of 16 years for the development of heart disease. Lp-PLA2 was an independent predictor of cardiac events, with a relative risk for patients in the second, third, and fourth quartiles of 1.66, 1.80, and 1.89, respectively, compared with the first quartile.

Most, but not all, observational studies reported a positive association of Lp-PLA2 with cardiovascular outcomes. Allison and colleagues (12) studied 508 patients with peripheral vascular disease followed for an average of 6.7 years. While there was a modest univariate association of Lp-PLA2 with cardiovascular events, this association disappeared after adjustment for established risk factors. In the Rotterdam Coronary Calcification Study, (13) similar results were reported. This population-based study followed 520 patients for seven years and evaluated the association between Lp-PLA2 and coronary calcification by electron-beam computed tomography scan. The unadjusted odds ratio (OR) for each standard deviation (SD) increase in Lp-PLA2 was 1.6 (95% CI: 1.1–2.4); however, this association became nonsignificant after controlling for lipid levels.

Some studies have specifically evaluated Lp-PLA2 as a risk factor in the diabetic population. For example, Saremi et al. (14) performed a substudy of the Veterans Affairs Diabetes trial (VADT) examining risk factors that predicted the progression of coronary artery calcification over an average of 4.6 years of follow-up. Lp-PLA2 mass was 1 of 2 significant independent predictors that remained ($p = 0.01$) after adjustment for standard risk factors. Hatoum et al. (15) evaluated Lp-PLA2 as a risk factor for incident coronary heart disease in 1,517 diabetic patients enrolled in the Health Profession Follow-Up Study. After adjustment for standard risk factors, the RR for incident CHD for the upper quartile of Lp-PLA2 activity compared to the lower quartile was 1.39 (95% CI: 1.01–1.90, $p = 0.03$).

Other studies have correlated Lp-PLA2 levels with different parameters of cardiovascular disease. Multiple publications have reported that Lp-PLA2 levels are associated with characteristics of “vulnerable atherosclerotic plaques,” both in the coronary (16) and in the carotid arteries (17). A subsequent publication also found an association between Lp-PLA2 levels and plaque rupture. (18)

A number of systematic reviews have been published that summarize the observational studies on the association of Lp-PLA2 and cardiovascular disease. (19–21) For example, Garza and colleagues (19) reviewed 14 observational studies enrolling 20,549 patients. This study reported the predictive ability of Lp-PLA2 levels for cardiovascular disease after adjustment for traditional cardiac risk factors. The combined odds ratio (OR) for an elevated Lp-PLA2 was reported as 1.60 (95% CI: 1.36–1.89) for the development of future cardiac events. A patient-level meta-analysis (20) evaluated the association between Lp-PLA2 levels, CAD, stroke, and mortality. A total of 79,036 participants from 32 prospective studies were included in this report. There were significant associations found between Lp-PLA2 and all three outcome measures. For every 1 SD increase in Lp-PLA2 levels, the RR adjusted for conventional risk factors was 1.10 (95% CI: 1.04–1.17) for CAD, 1.08 (95% CI: 0.97–1.20) for stroke, and 1.16 (95% CI: 1.09–1.24) for vascular death. There was also a significant association found between Lp-PLA2 levels and non-vascular deaths (RR: 1.10, 95% CI: 1.04–1.17). The authors estimated that this strength of association was similar to that seen for non-high-density lipoprotein (HDL) cholesterol and systolic blood pressure.

Numerous additional studies were identified that evaluated Lp-PLA2 as a risk factor for cardiovascular outcomes, including some that have been published more recently than the systematic reviews discussed above. (22, 23) The majority of these evaluated Lp-PLA2 as an independent risk factor for coronary disease in various patient populations.

Another study evaluated the discriminatory ability of Lp-PLA2 for incident CHD in 421 cases and 800 controls from the Nurses' Health Study. (24) Lp-PLA2 was a significant predictor of CHD after adjustment for traditional risk factors with a RR of 1.75 (95% CI: 1.09–2.84). It also added significantly to the discriminatory ability, as judged by an increase in the area under the curve from 0.720

without Lp-PLA2 to 0.733 with Lp-PLA2, and improved the net reclassification improvement index for discriminating between patients with and without CHD ($p=0.004$).

Conclusions

There is a large amount of evidence establishing that Lp-PLA2 levels are an independent predictor of cardiovascular risk factors, physiologic measures of cardiac disease, and cardiovascular events. This association has been demonstrated in a variety of clinical populations, in individuals both with and without cardiovascular disease. The evidence on the ability of Lp-PLA2 to reclassify patients into clinically relevant categories is less convincing, with the largest patient-level meta-analysis reporting no significant improvement.

LP-PLA2 as Treatment Target

Interventional studies involving Lp-PLA2 suggest that the level of Lp-PLA2 is modifiable by antihyperlipidemic drugs (e.g., statins, fibrates, and niacin). An ad hoc study of the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis In Myocardial Infarction) trial, (25) in which Lp-PLA2 levels were measured at baseline ($n=3,648$) and at 30 days ($n=3,265$) and patients were followed up for a mean of 24 months for death, MI, unstable angina, revascularization, or stroke, suggested that patients randomized to atorvastatin 80 mg/day, but not pravastatin 40 mg/day, experienced a 20% reduction of Lp-PLA2 levels at 30 days, independent of other cardiac risk factors. The 30-day, Lp-PLA2 level was independently associated with an increased risk of cardiovascular events. Another ad hoc study from the DIACOR (Diabetes and Combined Lipid Therapy Regimen) trial (26) demonstrated improved Lp-PLA2 levels (overall 16.8% reduction) compared to baseline, with no difference found between treatment groups among the 300 patients with diabetes and mixed dyslipidemias randomized to either fenofibrate 160 mg/day, simvastatin 20 mg/day, or both, for 12 weeks.

Rosenson randomized 55 hyperlipidemic subjects with metabolic syndrome to fenofibrate or placebo. (27) Fenofibrate treatment was associated with a 13% reduction in Lp-PLA2 mass compared to placebo. Saougos et al. studied the effect of three lipid-lowering agents, rosuvastatin, ezetimibe, and fenofibrate, on Lp-PLA2 levels. (28) All three agents significantly lowered Lp-PLA2 levels; fenofibrate also selectively increased HDL-associated Lp-PLA2 levels.

At least 2 clinical trials have examined the change in Lp-PLA2 levels in patients treated with statins versus placebo and evaluated whether the utility of Lp-PLA2 for risk stratification is modified by statin treatment. (29, 30) Ridker et al. analyzed the changes in Lp-PLA2 levels among patients in the JUPITER trial, a randomized controlled trial (RCT) of 17,802 individuals randomized to rosuvastatin or placebo. (29) Among patients assigned to rosuvastatin, Lp-PLA2 mass decreased by 33.8%. In the placebo group, Lp-PLA2 levels were predictive of subsequent cardiac events, but this was not true in the rosuvastatin group. In a similar analysis of the MIRACL RCT, Ryu et al. analyzed 2,587 patients treated with high-dose atorvastatin or placebo. (30) Atorvastatin reduced Lp-PLA2 levels in 2,587 patients treated with high-dose atorvastatin or placebo. Atorvastatin reduced Lp-PLA2 mass by 32.1% and Lp-PLA2 activity by 29.5%. In the placebo group, Lp-PLA2 levels were predictive of adverse cardiac outcomes, but no relationship was found in the atorvastatin group. The authors estimated that treatment with statins reduced the attributable risk of death due to Lp-PLA2 by approximately 50%.

Preliminary clinical trials of Lp-PLA2 inhibitors have been published, although none of the Lp-PLA2 inhibitors have been approved by the U.S. Food and Drug Administration (FDA) for any indication. Darapladib was the first drug of this class that was tested. Mohler et al. randomized 959 patients with hyperlipidemia receiving atorvastatin to placebo or one of 3 doses of darapladib. (29) Dose-dependent inhibition of Lp-PLA2 was noted, ranging from 43% to 66% compared with placebo. The inflammatory markers interleukin-6 and high-sensitivity C-reactive protein (hsCRP) were also reduced by 12.3% and 13%, respectively. Serruys et al. randomized 330 patients with documented coronary artery disease to darapladib or placebo, and reported the impact of 12 months of treatment with darapladib on Lp-PLA2 levels, hsCRP levels, and coronary plaque composition as measured by intravascular ultrasound (30). This study found no difference in plaque deformability, but a reduction in plaque necrotic core was reported for the darapladib group. Lp-PLA2 levels were decreased by 59%, but there were no significant differences in hsCRP levels between groups.

A second phospholipase A2, varespladib, is also being tested in early clinical trials. There are at least 2 phase III studies underway on these agents. (22) The STABILITY trial is a randomized, double-blind placebo-controlled trial of darapladib for patients with chronic CAD. The trial is projected to enroll over 15,000 patients from 800 clinical centers worldwide and report on the primary outcome of major adverse cardiovascular events. The FRANCIS-ACS trial is a randomized, double-blind, placebo-controlled trial of varespladib for patients with acute coronary syndrome. This trial is projected to enroll 700 patients, with follow-up for at least 24 weeks, and report on the primary endpoint of major cardiovascular events.

Trials of Lp-PLA2 continue to be ongoing. A third Phase III trial was identified using darapladib as treatment for CAD. (32) The Stabilization of plaques using Darapladib – Thrombolysis in Myocardial Infarction 52 (SOLID-TIMI 52) trial will enroll approximately 11,500 participants within 30 days of acute MI. Participants will be randomized to darapladib or placebo and followed for 3 years for the outcomes of cardiovascular death, nonfatal MI, or stroke. This trial is currently in the recruitment phase.

Conclusions

Levels of Lp-PLA2 decrease substantially following treatment with anti-lipid medications, including statins. However, there are not currently well-accepted thresholds for using Lp-PLA2 as a treatment target. Some studies have reported that treatment with statins eliminates the predictive ability of Lp-PLA2 as a treatment target; this may potentially reduce the potential of Lp-PLA2 for this purpose.

Inhibitors of Lp-PLA2 have been developed and tested in clinical trials, but no trials have demonstrated an improvement in health outcomes with these inhibitors. Further phase III clinical trials are ongoing.

Summary

There is a large body of literature evaluating lipoprotein-associated phospholipase A2 (Lp-PLA2) as a predictor of cardiovascular risk. These studies demonstrate that Lp-PLA2 is an independent predictor of cardiovascular disease but do not demonstrate that health outcomes are improved as a result of measuring Lp-PLA2. Improved risk prediction does not by itself result in improved health outcomes. To improve outcomes, clinicians must have the tools to incorporate emerging risk factors into existing risk prediction models, and these models should demonstrate improved classification into risk categories that will lead to more appropriate treatment. These tools are not currently available to the practicing clinician for Lp-PLA2. As a result, use of Lp-PLA2 for risk stratification for cardiovascular disease is considered investigational.

Clinical trials of Lp-PLA2 inhibitors are a new line of research with therapeutic potential. However, the available trials are preliminary, reporting only on physiologic outcomes such as reduction in high-sensitivity C-reactive protein (hsCRP), and use a pharmacologic agent that is not yet approved for use in the U.S. At least 3 Phase III clinical trials that utilize clinical outcomes as the primary endpoint (s) are currently in progress, and results from these may be available starting in 2012. Therefore, Lp-PLA2 has not demonstrated improved outcomes as a treatment target and is considered investigational for this purpose.

Practice Guidelines and Position Statements

The American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) published joint guidelines on the assessment of cardiovascular risk in asymptomatic patients in 2010. (35) The guidelines contained the following statement concerning testing for LpA-PLA2:

- Lipoprotein-associated phospholipase A2 might be reasonable for cardiovascular risk assessment in intermediate-risk asymptomatic adults. (Class IIb recommendation; Level of Evidence B)

The American Association of Clinical Endocrinologists (AACE) published guidelines for the management of dyslipidemia and prevention of atherosclerosis in 2012. (36) These guidelines made the following recommendations for LpA-PLA2 testing:

- Assess markers of inflammation in patients where further stratification of risk is necessary. Highly sensitive CRP and Lp-PLA2 provide useful information in these instances and appear to be synergistic in predicting risk of CVD and stroke. (Grade B recommendation; best level of evidence 1)
- Measure Lp-PLA2, which in some studies has demonstrated more specificity than highly sensitive CRP [hsCRP], when it is necessary to further stratify a patient's CVD risk, especially in the presence of systemic highly sensitive CRP elevations (Grade B recommendation; best level of evidence 2).

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Coding

[\[TOP\]](#)

Codes	Number	Description
CPT	83698	Lipoprotein-associated Phospholipase A ₂ (Lp-PLA ₂)
ICD-9 Procedure		
ICD-9 Diagnosis		Investigational for all codes
ICD-10-CM (effective 10/01/14)		
ICD-10-PCS (effective 10/01/14)		

HCPCS**Type of Service**

Medicine

Place of Service

Laboratory

Appendix[\[TOP\]](#)

N/A

History[\[TOP\]](#)

Date	Reason
01/13/04	Add to Medicine Section - New Policy
03/08/05	Replace Policy - Policy updated; references added; policy statement unchanged.
06/16/06	Replace Policy - Policy updated with literature search; policy statement unchanged, references added; update scope and disclaimer.
02/13/07	Replace Policy - Policy updated with literature review; references added. No change in policy statement.
05/08/07	Cross Reference Update - No other changes.
10/9/07	Cross Reference Update - No other changes.
01/8/08	Replace Policy - Policy updated with literature review; no change in policy statement; references added.
11/11/08	Replace Policy - Policy updated with literature search; no change in policy statement. References added.
11/10/09	Cross Reference Update - No other changes.
04/13/10	Replace Policy - Policy updated with literature search; no change in policy statement. Reference added.
08/10/10	Replace Policy - Policy updated with literature review; no changes in policy statement. The Rationale section has been extensively condensed and revised; reference numbers two, 15 and 22 have been added.
08/09/11	Replace Policy – Policy updated with literature search through April 2011; no changes to policy statement. References 16-18 and 26 were added.
08/20/12	Replace Policy. Policy updated with literature search through April 2012; no changes to policy statement. References 15-17, 20, 26 and 27 were added.
09/18/12	Update Coding Section – ICD-10 codes are now effective 10/01/2014.
08/16/13	Replace policy. Policy updated with literature search through May 15, 2013, references 22, 23 added. No change to policy statement.

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Lipoprotein-associated phospholipase A₂ activity improves risk discrimination of incident coronary heart disease among women

Ida J. Hatoum, ScD,^a Nancy R. Cook, ScD,^b Jeanenne J. Nelson, PhD,^c Kathryn M. Rexrode, MD,^b and Eric B. Rimm, ScD^{a,d} *Boston, MA, and Research Triangle, NC*

Background This study sought to determine the relation between and discriminative capability of lipoprotein-associated phospholipase A₂ (Lp-PLA₂) and coronary heart disease (CHD) in a large population of disease-free women.

Methods Among participants of the Nurses' Health Study who provided a blood sample, there were 421 cases of incident myocardial infarction during 14 years of follow-up. Controls were matched to cases 2:1 using risk set sampling based on age, smoking, and blood draw date.

Results After conditioning on the matching factors, Lp-PLA₂ activity was significantly associated with myocardial infarction (relative risk [RR] 2.86 for extreme quartiles, 95% CI 1.98-4.12). Upon additional adjustment for lipid, inflammatory, and clinical risk factors, the RR remained statistically significant (RR 1.75, 95% CI 1.09-2.84). The discriminative capability of Lp-PLA₂ was assessed by comparing the area below the receiver operating characteristic curves for models with and without Lp-PLA₂ and by calculating the net reclassification improvement index. The addition of Lp-PLA₂ activity to a multivariable-adjusted model increased the receiver operating characteristic curves from 0.720 to 0.733 and significantly improved the net reclassification improvement index ($P = .004$).

Conclusions Levels of Lp-PLA₂ activity were significantly associated with incident CHD among women. In addition, Lp-PLA₂ activity added significantly to CHD risk discrimination. (Am Heart J 2011;161:516-22.)

Heart disease is the leading cause of death for both men and women in industrialized countries.¹ Although several risk factors for heart disease have been identified, coronary heart disease (CHD) still occurs in people who lack any traditional risk factors.² The recognition that CHD is an inflammatory disease³ has led to the search for potential biomarkers that play a role in the etiology of CHD or serve as predictors of CHD risk. Such studies have examined several of these general inflammatory biomarkers including C-reactive protein,⁴ interleukin 6,⁵ and tumor necrosis factor α .⁶

One recently identified inflammatory biomarker, lipoprotein-associated phospholipase A₂ (Lp-PLA₂), is a

calcium-independent member of the superfamily of phospholipase A₂ enzymes. This 45.4-kd protein is secreted by monocytes, macrophages, T lymphocytes, and mast cells and binds to the carboxy terminus of apolipoprotein B-100 to circulate with low-density lipoprotein (LDL). Eighty percent of Lp-PLA₂ circulates bound to LDL with apparent binding preference for small, dense, and electronegative LDL.⁷ Lipoprotein-associated phospholipase A₂ hydrolyzes the *sn*2 ester bond of oxidized phospholipids to produce lysophosphatidacholine and nonesterified fatty acids,⁸ 2 inflammatory compounds that act within the intima of atherosclerotic lesions to perpetuate inflammation.⁸

Epidemiologic studies of circulating Lp-PLA₂ and cardiovascular disease have consistently demonstrated a positive association for both Lp-PLA₂ concentration⁹⁻¹¹ and Lp-PLA₂ activity¹¹⁻¹⁴ in both healthy populations^{10,12,13} and clinical populations.^{9,11,14} However, few of these studies of Lp-PLA₂ activity were in large healthy populations. Furthermore, few studies have characterized the predictive capability and potential clinical utility of Lp-PLA₂ activity.^{15,16}

Therefore, the aim of this study is to assess the association between Lp-PLA₂ activity and incident CHD in a large population of disease-free women. In addition,

From the ^aDepartment of Nutrition and Epidemiology, Harvard School of Public Health, Boston, MA, ^bDonald W. Reynolds Center for Cardiovascular Research and the Center for Cardiovascular Disease Prevention, Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA, ^cGlaxoSmithKline, Research Triangle, NC, and ^dChanning Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA.

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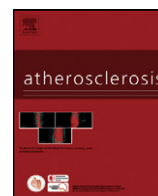
Reprint requests: Ida Hatoum, ScD, Harvard School of Public Health, 665 Huntington Ave, Boston, MA 02115.

E-mail: ihatoum@hsph.harvard.edu

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Lipoprotein-associated phospholipase A₂ testing usefulness among patients with symptomatic intracranial atherosclerotic disease

Andreu Massot^a, Dolors Pelegri^b, Anna Penalba^a, Juan Arenillas^c, Cristina Boada^a, Dolors Giralt^a, Marc Ribó^d, Carlos A. Molina^d, Anna Rosell^a, José Alvarez-Sabín^d, Pilar Chacón^e, Alex Rovira^f, Pilar Delgado^a, Joan Montaner^{a,d,*}

^a Neurovascular Research Laboratory, Department of Neurology, Autonomous University of Barcelona, Vall d'Hebron Hospital Barcelona, Spain

^b Clinical Biochemistry Unit, Department of Biochemistry, Autonomous University of Barcelona, Vall d'Hebron Hospital Barcelona, Spain

^c Neurovascular Unit, Stroke Unit and Neurology Department, Hospital Universitario de Valladolid, Valladolid, Spain

^d Neurovascular Unit, Department of Neurology, Autonomous University of Barcelona, Vall d'Hebron Hospital Barcelona, Spain

^e Lipid Research Unit, Department of Biochemistry, Autonomous University of Barcelona, Vall d'Hebron Hospital Barcelona, Spain

^f Magnetic Resonance Unit, Department of Neuroradiology, Autonomous University of Barcelona, Vall d'Hebron Hospital Barcelona, Spain

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ABSTRACT

Background and purpose: Circulating lipoprotein-associated phospholipase A₂ (Lp-PLA₂) has emerged as a novel biomarker for cardiovascular diseases. Our aim was to determine Lp-PLA₂ mass and activity in a selected cohort of first-ever transient ischemic attack (TIA) or ischemic stroke patients with intracranial atherosclerotic disease (ICAD) and to investigate its relationship with the presence of classical vascular risk factors, response to secondary prevention treatments and risk of recurrent vascular events.

Methods: Lp-PLA₂ mass and activity were measured 3 months after TIA or stroke by means of the PLAC test and CAM-assay (diaDexus, Inc.) respectively in 75 patients. Classic vascular risk factors, preventive treatments and clinical characteristics at the time of the index event were recorded. Follow-up transcranial Doppler ultrasonography (TCD) was performed and the presence of a new vascular event was assessed every 6 months.

Results: Several preventive treatments (statins and clopidogrel) were significantly associated with lower Lp-PLA₂ mass and activity. During follow-up (median time 23 months), eighteen patients (24%) suffered a new vascular event. Baseline factors associated with new vascular events were: history of coronary artery disease, number of intracranial stenoses detected by TCD and also Lp-PLA₂ activity, which was the only independent predictor for new vascular events (hazard ratio 2.89; 95% CI 1.029 to 8.096; $p = 0.044$) after multivariate analysis (Cox regression).

Conclusions: Lp-PLA₂ activity might be a useful tool to identify intracranial large-artery occlusive disease patients at higher risk of suffering new vascular events.

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1. Introduction

Intracranial atherosclerotic disease (ICAD) is an important cause of stroke worldwide being responsible of about 8% of strokes in Caucasian population and as far as one third of Chinese population strokes [1,2]. Almost a quarter (22%) of these patients will suffer other ischemic events over the next 2 years despite the best preventive treatments [3], a risk that has been related to the progression of intracranial stenoses [4].

This unacceptable prognosis could be improved through the identification of higher risk patients who could benefit from a more intensive preventive approach. In this regard, some inflammatory biomarkers such as C-reactive protein (CRP) have shown the ability to predict future cardiovascular events, ischemic stroke and progression of symptomatic ICAD [5,6].

Similarly, lipoprotein-associated phospholipase A₂ (Lp-PLA₂) has emerged as a novel cardiovascular risk marker which activity seems to be stable over time [7] and unaffected by systemic inflammatory stimulus [8].

Lp-PLA₂ is a calcium-independent phospholipase derived especially from macrophages, that circulates mainly bound to low density lipoproteins (LDL) in plasma and is responsible of LDL metabolism, producing two pro-inflammatory mediators such as lysophosphatidylcholine (lysoPC) and oxidized nonesterified fatty acids (oxNEFAs), which are able to activate inflammatory path-

* Corresponding author at: Neurovascular Research Laboratory, Neurovascular Unit, VHIR, Hospital Vall d'Hebron, Barcelona. Pg. Vall d'Hebron, 119-129, 08035 Barcelona, Spain. Tel.: +34 934894029; fax: +34 934894102.

E-mail address: 31862jmv@comb.cat (J. Montaner).

**AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS'
GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND
PREVENTION OF ATHEROSCLEROSIS**

*Paul S. Jellinger, MD, MACE; Donald A. Smith, MD, FACE;
Adi E. Mehta, MD, FRCP(C), FACE; Om Ganda, MD, FACE;
Yehuda Handelsman, MD, FACP, FACE; Helena W. Rodbard, MD, FACP, MACE;
Mark D. Shepherd, MD, FACE; John A. Seibel, MD, MACE;
the AACE Task Force for Management of Dyslipidemia and Prevention of Atherosclerosis*

American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice are systematically developed statements to assist health care professionals in medical decision-making for specific clinical conditions, but are in no way a substitute for a medical professional's independent judgment and should not be considered medical advice. Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment was applied.

These guidelines are a working document that reflects the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. We encourage medical professionals to use this information in conjunction with, and not as a replacement for, their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual patient circumstances.

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Abbreviations

AACE = American Association of Clinical Endocrinologists; **ATP** = Adult Treatment Panel; **apo** = apolipoprotein; **BEL** = best evidence level; **CAD** = coronary artery disease; **CPG** = clinical practice guidelines; **CRP** = C-reactive protein; **CVD** = cardiovascular disease; **EL** = evidence level; **HDL-C** = high-density lipoprotein cholesterol; **HRT** = hormone replacement therapy; **IMT** = intimal media thickness; **LDL-C** = low-density lipoprotein cholesterol; **Lp-PLA₂** = lipoprotein-associated phospholipase A₂; **MI** = myocardial infarction; **NCEP** = National Cholesterol Education Program; **QALY** = quality-adjusted life-year; **VLDL-C** = very low-density lipoprotein cholesterol

1. INTRODUCTION

Each year, an estimated 785 000 Americans will have a new coronary artery disease (CAD) event, and approximately 470 000 will have a recurrent attack. CAD caused approximately 1 of every 6 deaths in the United States in 2007. Although rates of stroke are declining, mortality data from 2007 indicate that stroke accounted for 1 of every 18 deaths in the United States. An estimated 33 600 000 adults 20 years or older have total serum cholesterol levels of 240 mg/dL or greater, for a prevalence of 15% of the American population (**1 [EL 3]**). Dyslipidemia is a primary, major risk factor for CAD and may even be a prerequisite for CAD, occurring before other major risk factors come into play. Epidemiologic data also suggest that hypercholesterolemia and perhaps coronary atherosclerosis itself are risk factors for ischemic stroke (**2 [EL 4]**). Increasing evidence also points to insulin resistance—which results in increased levels of plasma triglycerides and low-density lipoprotein cholesterol (LDL-C) and a decreased concentration of high-density lipoprotein cholesterol (HDL-C)—as an important risk factor for peripheral vascular disease (**3 [EL 3]**), stroke, and CAD (**4 [EL 3]**).

Analysis of 30-year national trends in serum lipid levels shows improvements in total cholesterol and LDL-C levels, which may in part be explained by the steady increase in the use of lipid-lowering drug therapy (self-reported rate of lipid-medication use, 38%). However, 69% of US adults have LDL-C concentrations above 100 mg/dL. Furthermore, the doubling in the prevalence of persons who are obese and the high percentage of patients with elevated triglyceride levels (33%) (and the correlation between obesity and elevated triglycerides) point to the need for continued vigilance on the part of physicians to reduce the risks of cardiovascular disease (**5 [EL 3]**).

These clinical practice guidelines (CPGs) are for the diagnosis and treatment of dyslipidemia and prevention

of atherosclerosis. The mandate for this CPG is to provide a practical guide for endocrinologists to reduce the risks and consequences of dyslipidemia. This CPG extends and updates existing CPGs available in the literature such as the American Association of Clinical Endocrinologists (AACE) Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Dyslipidemia and Prevention of Atherosclerosis (**6 [EL 4]**) and complements the Diabetes Mellitus Comprehensive Care Plan CPG (**7 [EL 4]**). The landmark National Cholesterol Education Program (NCEP) guidelines (**8 [EL 4]**) serve as the backbone of these lipid recommendations.

These guidelines are unique in that they support the use of apolipoprotein (apo) B or LDL particle number measurements to refine our efforts to achieve effective LDL-C lowering, provide screening recommendations for persons of different ages, and identify special issues for pediatric patients. They also touch on the unique challenges associated with atherosclerosis and heart disease in women. They continue to emphasize the importance of LDL-C lowering and support the measurement of inflammatory markers to stratify risk in certain situations. Finally, an evaluation of the cost-effectiveness of lipid-lowering therapy is presented.

This document is organized into discrete clinical questions, with responses in the Executive Summary and the full guidelines that provide the evidence base supporting these recommendations. The objectives of this CPG are to:

- Present an overview of the screening recommendations, assessment of risk, and treatment recommendations for various lipid disorders.
- Give special consideration for patients with diabetes, women, and pediatric patients who have dyslipidemia.
- Provide cost-effectiveness data to support treatment.

After this prefatory summary, a more in-depth scientific analysis of these issues is presented.

2. METHODS

This CPG was developed in accordance with the AACE Protocol for Standardized Production of Clinical Practice Guidelines—2010 Update (**9 [EL 4]**). Reference citations in the text of this document include the reference number, numerical descriptor (EL 1-4), and semantic descriptor (Table 1) (**9 [EL 4]**).

Recommendations are assigned evidence level (EL) ratings on the basis of the quality of supporting evidence (Table 2) (**9 [EL 4]**) all of which have also been rated for strength (Table 3) (**9 [EL 4]**). The format of this CPG is based on specific and relevant clinical questions. All primary writers have made disclosures regarding multiplicities

Consensus Panel Recommendation for Incorporating Lipoprotein-Associated Phospholipase A₂ Testing into Cardiovascular Disease Risk Assessment Guidelines

Michael H. Davidson, MD,^{a,b,*} Marshall A. Corson, MD,^c Mark J. Alberts, MD,^d
Jeffrey L. Anderson, MD,^e Philip B. Gorelick, MD,^f Peter H. Jones, MD,^g
Amir Lerman, MD,^h Joseph P. McConnell, PhD,ⁱ and Howard S. Weintraub, MD^j

A consensus panel was formed to review the rapidly emerging literature on the vascular-specific inflammatory marker lipoprotein-associated phospholipase A₂ (Lp-PLA₂) and to update recommendations for the appropriate use of this novel biomarker in clinical practice. The recommendations of the panel build on guidelines of the Adult Treatment Panel III (ATP III) and the American Heart Association/Centers for Disease Control (AHA/CDC) for cardiovascular risk assessment. Consistent with the ATP III guideline recommendations for the use of inflammatory markers, Lp-PLA₂ is recommended as an adjunct to traditional risk assessment in patients at moderate and high 10-year risk. A simplified framework for traditional Framingham risk factor assessment is proposed. As a highly specific biomarker for vascular inflammation, elevated Lp-PLA₂ levels should prompt consideration of increasing the cardiovascular risk category from moderate to high or high to very high risk, respectively. Because intensification of lifestyle changes and low-density lipoprotein (LDL) cholesterol lowering is beneficial in high-risk patients, regardless of baseline LDL cholesterol levels, consideration should be given to lowering the LDL cholesterol target by 30 mg/dL (1 mg/dL = 0.02586 mmol/L) in patients with high levels of Lp-PLA₂. Lp-PLA₂ is recommended as a diagnostic test for vascular inflammation to better identify patients at high or very high risk who will benefit from intensification of lipid-modifying therapies. However, at this time Lp-PLA₂ cannot be recommended as a target of therapy. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008; 101[suppl]:51F–57F)

The investigators met as a consensus panel to consider how lipoprotein-associated phospholipase A₂ (Lp-PLA₂) testing might be used in conjunction with guideline-endorsed cardiovascular disease (CVD) risk assessment

to identify which intermediate- and high-risk patients may be at even higher CVD risk, thereby justifying more aggressive risk-reducing strategies. The consensus panel endorses the testing of Lp-PLA₂ as an adjunct to traditional risk factor assessment to determine optimal lipid treatment goals commensurate with absolute risk. The consensus panel does not recommend measurement of Lp-PLA₂ a screening test in the general population or measurement in the low CVD risk population, but rather it recommends testing the estimated one third of adults classified as moderate risk based on Framingham risk criteria and the additional one quarter of adults classified as high CVD risk, based on objective measures of clinically manifest and sub/preclinical atherosclerotic CVD. The proposed framework is consistent with and builds on the Adult Treatment Panel III (ATP III) 2001 and 2004 guidelines, the 2003 American Heart Association/Centers for Disease Control (AHA/CDC) scientific statement on markers of inflammation and cardiovascular disease, and the AHA/American College of Cardiology (ACC) guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease.^{1–4}

^aPreventive Cardiology Center, University of Chicago, Pritzker School of Medicine, Chicago, Illinois, USA; ^bRadiant Research, Chicago, Illinois, USA; ^cDepartment of Medicine, University of Washington, Seattle, Washington, USA; ^dDepartment of Neurology, Northwestern University Medical School, Chicago, Illinois, USA; ^eCardiovascular Department, LDS Hospital, Salt Lake City, Utah, USA; ^fDepartment of Neurology and Rehabilitation, University of Illinois at Chicago College of Medicine, Chicago, Illinois, USA; ^gBaylor Lipid and Atherosclerosis Clinic, Baylor College of Medicine, Houston, Texas, USA; ^hDivision of Cardiovascular Disease, Mayo Clinic College of Medicine, Rochester, Minnesota, USA; ⁱDepartments of Cardiovascular Diseases and Laboratory Medicine, Immunochemical Core Laboratory, Mayo Clinic College of Medicine, Rochester, Minnesota, USA; and ^jDivision of Cardiology, Department of Medicine, New York University Medical Center, New York City, New York, USA.

Statement of author disclosure: Please see the Author Disclosures section at the end of this article.

*Address for reprints: Michael H. Davidson, MD, Preventive Cardiology Center, University of Chicago Pritzker School of Medicine, 515 North State Street, Suite 2700, Chicago, Illinois 60610.

E-mail address: MichaelDavidson@radiantresearch.com.

Lipoprotein-associated phospholipase A₂ and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies

The Lp-PLA₂ Studies Collaboration*

Summary

Background Lipoprotein-associated phospholipase A₂ (Lp-PLA₂), an inflammatory enzyme expressed in atherosclerotic plaques, is a therapeutic target being assessed in trials of vascular disease prevention. We investigated associations of circulating Lp-PLA₂ mass and activity with risk of coronary heart disease, stroke, and mortality under different circumstances.

Methods With use of individual records from 79 036 participants in 32 prospective studies (yielding 17 722 incident fatal or non-fatal outcomes during 474 976 person-years at risk), we did a meta-analysis of within-study regressions to calculate risk ratios (RRs) per 1 SD higher value of Lp-PLA₂ or other risk factor. The primary outcome was coronary heart disease.

Findings Lp-PLA₂ activity and mass were associated with each other ($r=0.51$, 95% CI 0.47–0.56) and proatherogenic lipids. We noted roughly log-linear associations of Lp-PLA₂ activity and mass with risk of coronary heart disease and vascular death. RRs, adjusted for conventional risk factors, were: 1.10 (95% CI 1.05–1.16) with Lp-PLA₂ activity and 1.11 (1.07–1.16) with Lp-PLA₂ mass for coronary heart disease; 1.08 (0.97–1.20) and 1.14 (1.02–1.27) for ischaemic stroke; 1.16 (1.09–1.24) and 1.13 (1.05–1.22) for vascular mortality; and 1.10 (1.04–1.17) and 1.10 (1.03–1.18) for non-vascular mortality, respectively. RRs with Lp-PLA₂ did not differ significantly in people with and without initial stable vascular disease, apart from for vascular death with Lp-PLA₂ mass. Adjusted RRs for coronary heart disease were 1.10 (1.02–1.18) with non-HDL cholesterol and 1.10 (1.00–1.21) with systolic blood pressure.

Interpretation Lp-PLA₂ activity and mass each show continuous associations with risk of coronary heart disease, similar in magnitude to that with non-HDL cholesterol or systolic blood pressure in this population. Associations of Lp-PLA₂ mass and activity are not exclusive to vascular outcomes, and the vascular associations depend at least partly on lipids.

Funding UK Medical Research Council, GlaxoSmithKline, and British Heart Foundation.

Introduction

Lipoprotein-associated phospholipase A₂ (Lp-PLA₂), an enzyme expressed by inflammatory cells in atherosclerotic plaques,^{1,2} is carried in the circulation bound predominantly to LDL.³ Lp-PLA₂ and other human A₂ phospholipases (such as secretory phospholipase A₂)⁴ propagate inflammation by producing precursors of arachidonic acid from membrane glycerophospholipids.⁵ Lp-PLA₂ (also called platelet-activating factor acetylhydrolase) hydrolyses oxidised phospholipids to yield pro-inflammatory products that are implicated in endothelial dysfunction, plaque inflammation, and formation of necrotic core in plaque,^{6,7} and is postulated to link oxidative modification of LDL and development of inflammatory responses in the arterial intima.^{8,9}

Since the initial report in 2000,¹⁰ many prospective epidemiological studies have investigated the associations between circulating Lp-PLA₂ (assayed either as its enzymatic activity or mass concentration) and subsequent risk of vascular disease outcomes. A meta-analysis of 14 such studies has been reported.¹¹ However, because that review was based on published data, it was unable to

provide detailed analyses (eg, separate examination of associations with coronary heart disease and stroke; characterisation of the shape of any dose-response relations) or to adjust consistently for potential confounding factors.

The objective of the Lp-PLA₂ Studies Collaboration,¹² an analysis of individual data from relevant prospective studies, was to assess the independence, specificity, magnitude, and shape of associations of Lp-PLA₂ with coronary heart disease, stroke, and mortality under different circumstances.

Methods

Study design

Details of study selection and data collection have been described previously.¹² Information about Lp-PLA₂ in relation to major vascular disease morbidity or cause-specific mortality was supplied by 32 prospective studies, 19 of which agreed to participate before their publication. Data were available for 79 036 participants (webappendix pp 2 and 17–20); only two relevant studies (comprising <5% of known incident vascular outcomes) were unable

Lancet 2010; 375: 1536–44

See Comment page 1498

*Members listed at end of paper

Correspondence to:

Lp-PLA₂ Studies Collaboration
Coordinating Centre,
Department of Public Health and
Primary Care, University of
Cambridge, Strangeways
Research Laboratory, Cambridge
CB1 8RN, UK
lsc@phpc.cam.ac.uk

See Online for webappendix

Section 8.0

Previously Discussed Items

Intraocular Steroid Implants

Question: How should the intraocular steroid implants be dealt with on the Prioritized List?

Question Source: VBBS

Issue: Intravitreal injections for certain eye conditions were reviewed at the August, 2013 VBBS meeting. At that meeting, there was testimony heard from Allergan regarding Ozurdex. HERC staff were instructed to consult with P&T committee about specific questions about Ozurdex and bring back revised recommendations. Please see the August meeting materials for the evidence reviewed on these treatments as well as the recommended code pairings.

Specific questions:

- 1) Did P&T review the evidence on Ozurdex as well as Retisert?
 - a. P&T response: yes
- 2) Should the requirement for systemic steroid use be in place of Ozurdex or just Retisert?
 - a. P&T response: Both should have the requirement of systemic AND local steroid use (these are 3rd line treatments)
- 3) Should Ozurdex or Retisert or both be used for retinal vein occlusion?
 - a. P&T response: only Ozurdex is effective for this condition
- 4) What are the harms of each treatment?
 - a. P&T response: both can cause increased intraocular pressure and glaucoma

HERC Staff Recommendations:

- 1) Chronic posterior uveitis is located on Line 106 DIABETIC AND OTHER RETINOPATHY. However, intraocular steroids should continue to not be covered for diabetic macular edema.
 - a. Add 67027 and 67028 to Line 106 for the April 1, 2014 Prioritized List
 - b. Add a guideline:

**GUIDELINE NOTE XXX INTRAOCULAR STEROID IMPLANTS
FOR CHRONIC NON-INFECTIOUS UVEITIS**

Line 106

Intraocular steroid implants (CPT 67027, 67028) are only included on Line 106 for pairing with uveitis (ICD-9 363.0x, 363.1x, 363.20, 363.22; ICD-10 H30.0x9, H30.1x9, H30.93, H30.819), and only when the following conditions are met: uveitis is chronic, non-infectious, and affecting the posterior segment of the eye, and there has been appropriate trial and failure, or intolerance of therapy, with local and systemic corticosteroids and/or immunosuppressive agents.

Intraocular Steroid Implants

- c. Add 67027 and 67028 to Line 363 CHORIORETINAL INFLAMMATION for the October 1, 2014 ICD-10 Prioritized List. No guideline is needed for this line. Do not add to the other two lines which split from line 106 (100, 273).
- 2) Add implantable intraocular steroids to the retinal vein occlusion line 465
VENOUS TRIBUTARY (BRANCH) OCCLUSION; CENTRAL RETINAL VEIN OCCLUSION Treatment: Laser Surgery
- a. Add 67028 to Line 465 (note, this line remains the same in ICD-10)
 - b. Rename the *Treatment*: ~~LASER SURGERY~~; SURGICAL AND LASER THERAPY
 - c. Add a guideline to lines 465
- GUIDELINE NOTE XXX INTRAOCULAR STEROID IMPLANTS FOR CENTRAL RETINAL VEIN OCCLUSION**
- Line 465*
- Intraocular steroid implants (CPT 67028) are only included on Line 465 for treatment of central retinal vein occlusion (ICD-9 362.35, ICD-10 H34.81x) in those individuals who have failed anti-VEGF therapy.
- 3) Add the following coding specification to line 413
- a. Coding specification: "CPT 67027 (Implantation of intravitreal drug delivery system) is included on this line for use with medications other than intraocular steroid implants."
 - b. CPT 67027 already is present on this line; ICD-9 363.21 (Pars planitis)/ICD-10 H30.23 would pair with this code. However, there is no evidence for use in types of uveitis other than posterior uveitis, which now pairs on line 106.
- 4) Do not add other suggested diagnoses to a line with pairing for 67027.
- a. No evidence found for effectiveness or other more specific codes are available for pairing

Tonsillectomy/CPAP/Sleep Apnea Guideline for Children

Question: How can we best modify the existing tonsillectomy and sleep apnea guidelines for children?

Question Source: HOSC/HSC; HERC staff; OHP Medical Directors; DMAP; Drs. Holger Link and Kyle Johnson, OHSU Sleep Medicine

Issues:

A revised sleep apnea guideline was reviewed at the May and August, 2013 VBBS meetings and has been discussed in 2 work group meetings. Workgroup participants include Dr. Holger Link (pulmonologist and sleep specialist, OHSU), Dr. Derek Lam (sleep medicine specialist, OHSU), Dr. Henry Milcuk (ENT and sleep medicine, OHSU), Dr. Tracy Muday (OHP medical director), Dr. John Sattenspiel (OHP medical director) and HERC staff.

The group discussion determined that some type of validated test should be required to make the diagnosis of OSA in children. The plans are finding the validated questionnaires to be useful, while polysomnography (PSG) remains the gold standard of diagnosis. Daytime symptoms should not be required, because such symptoms are taken into consideration with the validated test requirement. Previously, the guideline had differentiated mild, moderate, and severe sleep apnea. The group members did not feel that this distinction was helpful except for hospital management after surgery, and would require a sleep study to determine. There was discussion about whether to require PSG prior to surgery for high risk children, including young children (under age 3). It was thought that a high risk child with history and exam consistent with OSA may not benefit from a PSG and that it was not a good use of OHP resources to require it. The decision was to encourage PSGs in this group, but not require them. However, the specialists felt that children with a history inconsistent with physical exam should have a sleep study to more fully determine the diagnosis.

The workgroup discussed how to define “child.” Age 18 was determined to be the best cut off, due to the definition of child in other guidelines, and due to the physiology of adolescents being different from adults.

Further discussions fine-tuned the definition of a positive PSG. There was concern with using an AHI cutoff of 5 or greater, as a recent study in the NEJM (the CHAT study) found that children who benefitted from tonsillectomy had a median AHI of 4.8. In that study, criteria for diagnosing OSA was an AHI>1. The group determined that an AHI>1 with a history and exam consistent with OSA would be the best diagnostic criteria.

The workgroup discussed the use of nocturnal polyoximetry for diagnosis of OSA. It was noted that the positive predictive value of this test is high, but the negative predictive value is low. About 25% of children go straight to surgery after this test; the other 75% require other testing to confirm or rule out OSA. Muday reported that this test is very inexpensive or free for her health plan. The experts raised concerns about artifacts making this test look positive, and the ability of home health agencies to get the correct

Tonsillectomy/CPAP/Sleep Apnea Guideline for Children

modalities on the testing equipment. The group determined that this test should be included as a diagnostic option as it is very low cost and may reduce the number of needed PSGs.

The workgroup discussed the requirement for evidence of compliance for continued CPAP coverage. The experts were concerned about children who were adapting to the CPAP machine/mask and did not yet have the required compliance. The medical directors assured the experts that their plans would approve continued use as long as a plan was in place to improve/address compliance.

Tonsillectomy/CPAP/Sleep Apnea Guideline for Children

Recommendations:

- 1) Add CPT 94660 (Continuous positive airway pressure ventilation (CPAP), initiation and management) to line 210
- 2) Add 94660 to line 210
- 3) Adopt a new guideline for pediatric sleep apnea diagnosis and treatment as shown below
- 4) Modify the existing Tonsillectomy Guideline and Sleep Apnea Guideline as shown below

GUIDELINE NOTE XXX, OBSTRUCTIVE SLEEP APNEA DIAGNOSIS AND TREATMENT FOR CHILDREN

Line 210

Obstructive sleep apnea (OSA) in children (18 or younger) must be diagnosed by

- 1) nocturnal polysomnography with an AHI >5 episodes/h or AHI>1 episodes/h with history and exam consistent with OSA, OR
- 2) nocturnal pulse oximetry with 3 or more SpO2 drops <90% and 3 or more clusters of desaturation events, or alternatives desaturation (>3%) index >3.5 episodes/h, OR
- 3) use of a validated questionnaire (such as the Pediatric Sleep Questionnaire or OSA 18), OR
- 4) consultation with a sleep medicine specialist.

Polysomnography and/or consultation with a sleep medicine specialist to support the diagnosis of OSA and/or to identify perioperative risk is recommended for

- 1) high risk children (i.e. children with cranio-facial abnormalities, neuromuscular disorders, Down syndrome, etc.)
- 2) children with equivocal indications for adenotonsillectomy (such as discordance between tonsillar size on physical examination and the reported severity of sleep-disordered breathing),
- 3) children younger than three years of age

Adenotonsillectomy is an appropriate first line treatment for children with OSA. Weight loss is recommended in addition to other therapy in patients who are overweight or obese. Intranasal corticosteroids are an option for children with mild OSA in whom adenotonsillectomy is contraindicated or for mild postoperative OSA.

CPAP is covered for a 3 month trial for children through age 18 who have

- 1) undergone surgery or are not candidates for surgery, AND
- 2) have documented residual sleep apnea symptoms (sleep disruption and/or significant desaturations) with residual daytime symptoms (daytime sleepiness or behavior problems)

CPAP will be covered for children through age 18 on an ongoing basis if:

- 1) There is documentation of improvement in sleep disruption and daytime sleepiness and behavior problems with CPAP use

Tonsillectomy/CPAP/Sleep Apnea Guideline for Children

- 2) Annual re-evaluation for CPAP demonstrates ongoing clinical benefit and compliance with use, defined as use of CPAP for at least four hours per night on 70% of the nights in a consecutive 30 day period

GUIDELINE NOTE 36, ADENOTONSILLECTOMY FOR INDICATIONS OTHER THAN OBSTRUCTIVE SLEEP APNEA

Lines 49, 84, ~~210~~, 395, 574

Tonsillectomy/adenotonsillectomy is an appropriate treatment for patients with:

1. Five documented attacks of strep tonsillitis in a year or 3 documented attacks of strep tonsillitis in each of two consecutive years where an attack is considered a positive culture/screen and where an appropriate course of antibiotic therapy has been completed;
2. Peritonsillar abscess requiring surgical drainage;
3. ~~Moderate or severe obstructive sleep apnea (OSA) in children 18 and younger, or mild OSA in children with daytime symptoms and/or other indications for surgery. For children 3 and younger or for children with significant co-morbidities, OSA must be diagnosed by nocturnal polysomnography. For children older than 3 who are otherwise healthy, OSA must be diagnosed by either nocturnal polysomnography, use of a validated questionnaire (such as the Pediatric Sleep Questionnaire or OSA-18), or consultation with a sleep medicine specialist; or,~~
4. ~~3.~~ Unilateral tonsillar hypertrophy in adults; unilateral tonsillar hypertrophy in children with other symptoms suggestive of malignancy.

See Guideline Note XXX for diagnosis and treatment of obstructive sleep apnea in children

GUIDELINE NOTE 27, SLEEP APNEA

Line 210

Surgery for sleep apnea for adults (18 and older) is only covered after documented failure of both CPAP and an oral appliance.

ORIGINAL ARTICLE

A Randomized Trial of Adenotonsillectomy for Childhood Sleep Apnea

Carole L. Marcus, M.B., B.Ch., René H. Moore, Ph.D., Carol L. Rosen, M.D.,
Bruno Giordani, Ph.D., Susan L. Garetz, M.D., H. Gerry Taylor, Ph.D.,
Ron B. Mitchell, M.D., Raouf Amin, M.D., Eliot S. Katz, M.D., Raanan Arens, M.D.,
Shalini Paruthi, M.D., Hiren Muzumdar, M.D., David Gozal, M.D.,
Nina Hattiangadi Thomas, Ph.D., Janice Ware, Ph.D., Dean Beebe, Ph.D.,
Karen Snyder, M.S., Lisa Elden, M.D., Robert C. Sprecher, M.D., Paul Willging, M.D.,
Dwight Jones, M.D., John P. Bent, M.D., Timothy Hoban, M.D.,
Ronald D. Chervin, M.D., Susan S. Ellenberg, Ph.D.,
and Susan Redline, M.D., M.P.H., for the Childhood Adenotonsillectomy Trial (CHAT)

ABSTRACT

BACKGROUND

Adenotonsillectomy is commonly performed in children with the obstructive sleep apnea syndrome, yet its usefulness in reducing symptoms and improving cognition, behavior, quality of life, and polysomnographic findings has not been rigorously evaluated. We hypothesized that, in children with the obstructive sleep apnea syndrome without prolonged oxyhemoglobin desaturation, early adenotonsillectomy, as compared with watchful waiting with supportive care, would result in improved outcomes.

METHODS

We randomly assigned 464 children, 5 to 9 years of age, with the obstructive sleep apnea syndrome to early adenotonsillectomy or a strategy of watchful waiting. Polysomnographic, cognitive, behavioral, and health outcomes were assessed at baseline and at 7 months.

RESULTS

The average baseline value for the primary outcome, the attention and executive-function score on the Developmental Neuropsychological Assessment (with scores ranging from 50 to 150 and higher scores indicating better functioning), was close to the population mean of 100, and the change from baseline to follow-up did not differ significantly according to study group (mean $\pm$ SD] improvement, 7.1 ± 13.9 in the early-adenotonsillectomy group and 5.1 ± 13.4 in the watchful-waiting group; $P=0.16$). In contrast, there were significantly greater improvements in behavioral, quality-of-life, and polysomnographic findings and significantly greater reduction in symptoms in the early-adenotonsillectomy group than in the watchful-waiting group. Normalization of polysomnographic findings was observed in a larger proportion of children in the early-adenotonsillectomy group than in the watchful-waiting group (79% vs. 46%).

CONCLUSIONS

As compared with a strategy of watchful waiting, surgical treatment for the obstructive sleep apnea syndrome in school-age children did not significantly improve attention or executive function as measured by neuropsychological testing but did reduce symptoms and improve secondary outcomes of behavior, quality of life, and polysomnographic findings, thus providing evidence of beneficial effects of early adenotonsillectomy. (Funded by the National Institutes of Health; CHAT ClinicalTrials.gov number, NCT00560859.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Redline at Brigham and Women's Hospital, 221 Longwood Ave., Boston, MA 02115, or at sredline@partners.org.

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Night-to-Night Consistency of At-Home Nocturnal Pulse Oximetry Testing for Obstructive Sleep Apnea in Children

Martino Pavone, MD,^{1*} Renato Cutrera, MD, PhD,¹ Elisabetta Verrillo, MD,¹ Teresa Salerno, MD,¹ Serena Soldini,¹ and Robert T. Brouillette, MD²

Summary. Rationale: At-home nocturnal pulse oximetry has a high positive predictive value (PPV) for polysomnographically-diagnosed obstructive sleep apnea (OSA) but no studies have been published testing the night-to-night consistency of at-home nocturnal pulse oximetry for the evaluation of suspected OSA in children. We therefore determined the night-to-night consistency of nocturnal pulse oximetry as a diagnostic test for OSA in children. Methods: We prospectively studied 148 children (96 male) aged 4.9 ± 2.4 (1.2–11.8) years, referred for suspected OSA. To evaluate night-to-night consistency, we compared an oximetry analysis method, the McGill Oximetry Score (MOS), from two consecutive at-home nocturnal pulse oximetry recordings. Results: Pulse oximetry metrics were similar on the two nights. The MOS on the two nights showed excellent night-to-night consistency when analyzed as positive for OSA versus inconclusive, 143/148 (Spearman's correlation coefficient = 0.90). A more detailed analysis using four categories (MOS 1, 2, 3, and 4) of OSA severity showed very good night-to-night agreement, 133/148 (Spearman's correlation coefficient = 0.91). Variability was increased in children younger than 4 years of age compared to older children. Conclusions: Night-to-night consistency of nocturnal pulse oximetry as a diagnostic test for OSA showed excellent agreement. Night-to-night consistency of pulse oximetry, as analyzed by the MOS, for diagnosis and severity evaluation further validates this abbreviated testing method for pediatric OSA. Polysomnography (PSG) is required to rule in or rule out OSA in children if a single night oximetry testing is inconclusive. *Pediatr Pulmonol.* 2013; 48:754–760. © 2013 Wiley Periodicals, Inc.

Key words: night-to-night variability; pulse oximetry; obstructive sleep apnea.

Funding source: none reported.

INTRODUCTION

Obstructive Sleep Apnea (OSA) in children is a disorder of breathing characterized by partial and/or intermittent complete upper airway obstruction that disrupts normal ventilation during sleep and normal sleep patterns.¹ OSA affects about 1–4% of children.^{2,3} The main risk factors are adenotonsillar hypertrophy, obesity, craniofacial anomalies, and neuromuscular disease.^{3,4} Commonly reported symptoms include snoring, labored breathing, witnessed apneas, disturbed sleep, and daytime neurobehavioral problems. Complications include neurocognitive impairment, behavioral, cardiovascular, and metabolic problems.^{5,6} Nocturnal polysomnography (PSG) in a sleep laboratory represents the gold standard for the diagnosing of OSA but is costly and time-consuming.^{1,7}

Due to these difficulties, some pediatric centers begin testing for OSA with an abbreviated modality such as pulse oximetry or home PSG.⁸ Pulse oximetry is an increasingly used abbreviated testing modality for the evaluation of children with suspected OSA.^{9–11}

Normative data¹² and technical comparison between different devices have been published.¹³ Brouillette et al.⁹ demonstrated that an abnormal nocturnal pulse oximetry had a 97% positive predictive value (PPV) for detecting moderate to severe OSA when compared with

¹Respiratory Unit, Department of Pediatrics, Bambino Gesù Children's Hospital, Piazza S. Onofrio, Rome, Italy.

²Department of Pediatrics, McGill University and the McGill University Health Center Research Institute at the Montréal Children's Hospital Montreal, Canada.

*Correspondence to: Martino Pavone, MD, Respiratory Unit, Department of Pediatrics, Bambino Gesù Research Institute, Piazza S. Onofrio 4, 00165 Rome, Italy. E-mail: martino.pavone@opbg.net

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Nocturnal Pulse Oximetry as an Abbreviated Testing Modality for Pediatric Obstructive Sleep Apnea

Robert T. Brouillette, Angela Morielli, Andra Leimanis, Karen A. Waters, Rina Luciano and Francine M. Ducharme

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Nocturnal Pulse Oximetry as an Abbreviated Testing Modality for Pediatric Obstructive Sleep Apnea

Robert T. Brouillette, MD*; Angela Morielli, MBA, RPSGT*; Andra Leimanis, BSc*
Karen A. Waters, MBBS, PhD‡; Rina Luciano, RRT*; and Francine M. Ducharme, MD*

ABSTRACT. *Objective.* To determine the utility of pulse oximetry for diagnosis of obstructive sleep apnea (OSA) in children.

Methods. We performed a cross-sectional study of 349 patients referred to a pediatric sleep laboratory for possible OSA. A mixed/obstructive apnea/hypopnea index (MOAHI) greater than or equal to 1 on nocturnal polysomnography (PSG) defined OSA. A sleep laboratory physician read nocturnal oximetry trend and event graphs, blinded to clinical and polysomnographic results. Likelihood ratios were used to determine the change in probability of having OSA before and after oximetry results were known.

Results. Of 349 patients, 210 (60%) had OSA as defined polysomnographically. Oximetry trend graphs were classified as positive for OSA in 93 and negative or inconclusive in 256 patients. Of the 93 oximetry results read as positive, PSG confirmed OSA in 90 patients. A positive oximetry trend graph had a likelihood ratio of 19.4, increasing the probability of having OSA from 60% to 97%. The median MOAHI of children with a positive oximetry result was 16.4 (7.5, 30.2). The 3 false-positive oximetry results were all in the subgroup of 92 children who had diagnoses other than adenotonsillar hypertrophy that might have affected breathing during sleep. A negative or inconclusive oximetry result had a likelihood ratio of .58, decreasing the probability of having OSA from 60% to 47%. Interobserver reliability for oximetry readings was very good to excellent ($\kappa = .80$).

Conclusions. In the setting of a child suspected of having OSA, a positive nocturnal oximetry trend graph has at least a 97% positive predictive value. Oximetry could: 1) be the definitive diagnostic test for straightforward OSA attributable to adenotonsillar hypertrophy in children older than 12 months of age, or 2) quickly and inexpensively identify children with a history suggesting sleep-disordered breathing who would require PSG to elucidate the type and severity. A negative oximetry result cannot be used to rule out OSA. *Pediatrics* 2000;105:405–412. predictive value of tests, polysomnography, likelihood ratio, sleep apnea syndromes, questionnaire, sleep.

ABBREVIATIONS. OSA, obstructive sleep apnea; PSG, polysomnography; Sao₂, hemoglobin saturation; MOAHI, mixed/obstruc-

tive apnea/hypopnea index; REM, rapid eye movement.

Obstructive sleep apnea (OSA) in children is a disorder of breathing during sleep characterized by upper airway obstruction that disturbs sleep and disrupts normal respiratory gas exchange.^{1–3} Sequelae of OSA, including growth failure, cor pulmonale, and developmental delay, are thought to be attributable to sleep disturbance and repetitive hypoxemia.^{1,4,2} Ali et al⁵ estimated the prevalence of OSA in 4- to 5-year-old children at .7%, whereas 7% to 9% of children have simple snoring, a milder form of sleep-related upper-airway obstruction.^{5–7} Usually, pediatric OSA is attributable to adenotonsillar hypertrophy.

The most accurate and comprehensive method of diagnosing OSA is nocturnal polysomnography (PSG).³ Unfortunately, such testing is expensive and time-consuming. Thus, an abbreviated testing modality would be very helpful. We originally proposed that parental responses to questions about snoring, difficulty breathing during sleep, and observed obstructive apnea might distinguish normal children from those with OSA.⁸ However, several subsequent studies indicated that questionnaire responses could not reliably distinguish children with OSA from those with simple snoring.^{9–12}

Pediatric OSA sometimes, but not always, results in dips in hemoglobin saturation (Sao₂). In adults being evaluated for OSA, apparently conflicting results on the usefulness of pulse oximetry have been reported.^{13,14} For adults with a low pretest probability of OSA, a negative oximetry result may be sufficient to exclude the diagnosis; for adults with a high pretest probability of OSA, a positive oximetry result may be sufficient to confirm the diagnosis of OSA.¹⁵ The accuracy of nocturnal pulse oximetry compared with PSG for diagnosing pediatric OSA has not been evaluated.

Since 1993, when patients were referred to our pediatric sleep laboratory, we have: 1) had the parents complete a questionnaire, 2) performed nocturnal PSG, and 3) printed the pulse oximetry trend and event graphics that summarize nocturnal oxygenation status.^{8,16,17} The purpose of the current report is to assess, from this large series of referrals to our pediatric sleep laboratory, the potential utility of nocturnal pulse oximetry for diagnosing pediatric OSA. A secondary aim was to

From the *Department of Pediatrics, Montreal Children's Hospital, McGill University, Montreal, Canada; and the ‡Department of Respiratory Medicine, New Children's Hospital, University of Sydney, Sydney, Australia. Received for publication Mar 19, 1999; accepted Jul 22, 1999.

Reprint requests to (R.T.B.) Montreal Children's Hospital, 2300 Tupper St, Montreal, Quebec, Canada H3H 1P3. E-mail: robert.brouillette@muhc.mcgill.ca

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