



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

January 10, 2013

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

Section 1

Agenda

AGENDA
VALUE-BASED BENEFITS SUBCOMMITTEE
January 10, 2013
9:00am - 1:00pm

Meridian Park Room 117B&C
Community Health Education Center
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 | 9:00 AM |
| II. | Staff report – Ariel Smits, Cat Livingston, Darren Coffman | 9:05 AM |
| III. | Straightforward
A. Coronary brachytherapy | 9:15 AM |
| IV. | New discussion items
A. External elements exposure issues
B. Stereotactic radiation therapy for intracranial AVMs
C. Personal history of cancer V codes | 9:30 AM |
| V. | Previous Discussion Items
A. Other December follow up
A. Auricular acupuncture
B. Enzyme replacement therapy
A. Gaucher's disease
C. Silver compounds for caries treatment | 10:00 AM |
| VI. | Coverage guidances
A. Viscosupplementation for osteoarthritis of the knee
B. Percutaneous interventions for low back pain
C. Management of chronic otitis media in children | 11:30 AM |
| VII. | Guidelines
A. Immunization table/Prevention tables
B. Expensive/marginally effective drug guideline
C. Guideline Note 37 abnormal reflexes radiculopathy | 12:15 AM |
| VIII. | Public comment | 12:55 PM |
| IX. | Adjournment – Lisa Dodson | 1:00 PM |

Section 2

Minutes

Value-based Benefits Subcommittee Recommendations Summary For Presentation to: Health Evidence Review Commission on 1/10/13

For specific coding recommendations and guideline wording, please see the text of the 12/13/12 VbBS minutes.

CODE MOVEMENT

- The 2013 CPT, HCPCS, and CDT codes were placed as shown in Attachment A. These proposed placements will be placed on the HERC website to be available for viewing by the various health plans. Final approval of these placements will be done at the HERC meeting on January 10, 2013. These codes will appear on the April 1, 2013 Prioritized List as approved by the HERC in January.
- A missing tympanostomy tube removal procedure code was added to the acute mastoiditis line
- Tympanostomy procedure codes that were mistakenly not removed from the hearing loss line were removed
- A pharyngoplasty procedure code was added to the line with congenital neck problems

ITEMS CONSIDERED BUT NO CHANGES MADE

- The use of silver compounds for treatment of dental caries was discussed but no decision regarding coverage was reached
- The prioritization of pseudobulbar affect was discussed but no decision was reached
- A prenatal genetic testing guideline was discussed, and a work group will be convened to write it
- Changes to the guideline for hysterectomy for menstrual bleeding disorder were discussed, and will be readdressed at a future meeting

GUIDELINE CHANGES

- The coding specifications regarding cognitive behavioral therapy for low back pain were changed to indicate the correct CPT code
- Mistakes in the coding specification for bariatric surgery on the type 2 diabetes line were corrected
- The non-prenatal genetic testing guideline was modified to reflect changes needed for the new 2013 CPT genetic testing codes, as shown in Appendix C
- Two dental guidelines were modified and one deleted as shown in Appendix C
- The chronic otitis media with effusion treatment guideline was modified as shown in Appendix C
- A new guideline allowing coverage of puberty suppression in adolescents under new gender dysphoria line was adopted for the ICD-10 (October 2014) Prioritized List as shown in Appendix B

VALUE-BASED BENEFITS SUBCOMMITTEE
Meridian Park Health Education Center
December 13, 2012
8:30 AM – 2:30 PM

Members Present: Lisa Dodson, MD, Chair; Kevin Olson, MD, Vice-chair; Chris Kirk, MD; James Tyack, DMD; David Pollack MD; Mark Gibson; Irene Crosswell RPh; Laura Ocker, LAc; Susan Williams, MD.

Members Absent: none

Staff Present: Darren Coffman; Ariel Smits, MD, MPH; Cat Livingston, MD, MPH; Jason Gingerich; Dorothy Allen.

Also Attending: Denise Taray, DMAP; Kristi Jacobo, DMAP; Dr. Wally Shaffer, DMAP; David Fischer, AMH; Dr. Bruce Boston, OHSU Pediatric Endocrinology; Dr. Karin Selva, Legacy Pediatric Endocrinology; Jenn Burleton, Transactive; Dr. Ericka King, OHSU Pediatric Otolaryngology; Camille Kerr, Allergan; Gary Allen, DMD, Advantage Dental; Christina Schad, MD, and Julie Brown, Avenir Pharmaceuticals; Steven Duffin, Oral Health Outreach; Beryl Fletcher, ODA; Deborah Loy, Capital Dental; Aubrey Harrison, Basic Rights Oregon.

Roll Call/Minutes Approval/Staff Report

The meeting was called to order at 8:35 am and roll was called. Dr. Williams, an orthopedic surgeon practicing in Roseburg, was introduced as a new member of the subcommittee. Minutes from the 10/11/12 VbBS meeting were reviewed and approved with one change requested by Pollack regarding his remarks on the treatment resistant depression section.

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

Coffman shared the work of a group that is trying to make the coverage guidance process more efficient and more reflective of the actual authority of these guidances. There was a general discussion about what authority the guidances and Prioritized List guidelines have. The HERC has the authority to prioritize conditions, and the Legislature determines the coverage level. Other insurers or other bodies may or may not choose to follow these guidances.

Straightforward Discussion

➤ Topic: Straightforward Issues Table

Discussion: Smits introduced a document with straightforward coding changes. There was no discussion.

Actions:

- 1) Add 69424 to line 178.
- 2) Remove 69424 and 69433 from line 383
- 3) Add 42950 to line 71

➤ Topic: Low Back Pain Coding Specifications

Discussion:

Smits introduced a document with changes needed for the low back pain line coding specifications. There was no discussion.

Actions:

- 1) Add the following coding recommendation to Line 400 for the April 1, 2013 Prioritized List
 - a. Cognitive behavioral therapy (90785-90840) only pairs on Line 400 with the low back diagnoses (344.60, 722.1, 722.2, 722.7, 724.4)
- 2) Add the following coding recommendation to Line 562 for the April 1, 2013 Prioritized List
 - a. Cognitive behavioral therapy (90785-90840) only pairs on Line 562 with the low back diagnoses (720.2, 721.3, 721.7, 721.8, 721.90, 722.1, 722.2, 722.32, 722.39, 722.5, 722.6, 722.8, 722.9, 724.1, 724.2, 724.5-724.9, 739.2-739.4, 847.1-847.9).
- 3) Change the following coding recommendation for Line 400 for the April 1, 2013 Prioritized List
 - a. Cognitive behavioral therapy ([90785-90840](#)) only pairs on Line 400 with the low back diagnoses (344.60, 722.1, 722.2, 722.7, 724.4)
- 4) Change the following coding recommendation for Line 562 for the April 1, 2013 Prioritized List
 - a. Cognitive behavioral therapy ([90785-90840](#)) only pairs on Line 562 with the low back diagnoses (720.2, 721.3, 721.7, 721.8, 721.90, 722.1, 722.2, 722.32, 722.39, 722.5, 722.6, 722.8, 722.9, 724.1, 724.2, 724.5-724.9, 739.2-739.4, 847.1-847.9).

➤ **Topic: Bariatric Surgery Coding Specification**

Discussion: Smits introduced a document with changes needed for the bariatric surgery line coding specifications on the April 1, 2013 list. There was no discussion.

Actions:

1) The coding specification for line 33 was changed to read:

CPT codes 43644-43645 and 43846-43848 (Roux-En-Y gastric bypass) and 43770-43774⁵ (laparoscopic adjustable gastric banding) are only included on this line as treatment according to the requirements in Guideline Note 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-V85.40⁵ (BMI \geq 35).

New Codes 2013

➤ **Topic: 2013 CPT codes**

Discussion: Smits introduced several documents with recommendations for the placement of the 2013 CPT, CDT and HPCPS codes. These recommendations were accepted as shown in the meeting materials (see Appendix A), with the exceptions below. Other code changes recommended in the various issue documents were also accepted as shown in the meeting materials unless noted below. This discussion section includes the genetic testing and psychiatric CPT codes.

- 1) 52287 (chemodenervation of the bladder). The subcommittee altered the suggested guideline for this procedure to clarify that it was to be used for overactive bladder caused by several types of spinal diseases and that a patient must have failed appropriate pharmacologic management first rather than antimuscarinic medications, as there may be other types of appropriate medication.
- 2) 64615 (Chemodenervation for migraine). This code is recommended to be added to the Excluded File as suggested by staff. There was considerable discussion about the differing recommendations of trusted sources (MED vs NICE). There was some discussion about these sources possibly using different studies or having differing amounts of industry and patient/provider input. Livingston said the MED report found studies with statistically significant differences with botulinum therapy, but that these differences were

not clinically significant. Dodson noted that this treatment might be cost effective if it lowered ER costs/utilization. Croswell as noted that chronic migraine patients are not very functional, and any therapy that would allow them to be more productive should be considered. Gibson recommended not covering due to lack of clinically significant outcomes. Kirk felt that this therapy was not medically appropriate based on the evidence. Payers could make exceptions for high ER utilizing patients if the payer felt that this might decrease their overall costs. Shaffer noted that this exception could not be made for FFS patients if the treatment was placed on the Excluded File. Livingston reviewed GRADE criteria and noted that this therapy would likely not be recommended for coverage using this criteria. The decision was made to not cover.

- 3) 81235 (EGFR (epidermal growth factor receptor) testing). The subcommittee recommended placing on the line which included the diagnosis of non-small cell lung cancer (line 278), as this is the diagnosis for which this code is utilized (not the Diagnostic File). Olson noted that this procedure is a test on tumor tissue, not germ line tissue and therefore is not a genetic test. It therefore should not be included in the non-prenatal genetic testing guideline and that portion of the suggested guideline changes was not accepted.
- 4) 86152/86153 (Cell enumeration using immunologic selection) were recommended for placement on the Excluded File rather than the Diagnostic File. Olson stated that these tests are expensive and their place in cancer care is dubious. He recommended against coverage
- 5) 86711 (JC virus antibody) was placed on the multiple sclerosis and Crohn's disease lines (35 and 268) rather than the Diagnostic File. Livingston reported that this test is only FDA approved for use in these 2 indications. The subcommittee was concerned about over use for other indications without evidence of benefit.
- 6) 90839/90840 (psychotherapy for crisis) were not added to the low back pain lines (400 and 562)
- 7) 90863 (pharmacologic management) was recommended for addition to the Excluded File as this applies only to prescribed psychologists in 2 states (not Oregon). AMH suggested leaving this code open to allow for non-MD and non-NP mental health providers to bill for medication management. Pollack felt that this code was inappropriate for Oregon, as psychologists do not have prescribing privileges here.
- 8) 95782/95783 (pediatric polysomnography) are recommended to be placed on the Diagnostic File rather than the Ancillary File, because the subcommittee felt that these tests are used in the diagnosis of obstructive sleep apnea and other sleep issues. Pollack asked HERC staff to consider moving all polysomnography CPT codes from the Ancillary File to the Diagnostic File
- 9) The "C" HCPCS codes did not have placement determined. These codes are used solely during hospitalization and have never been included on the Prioritized List. There was discussion about the C codes for drug eluting cardiac stents. HERC staff was asked to consider having HTAS review drug eluting vs bare metal cardiac stent technology.

- 10) S8930 (electrical stimulation of auricular acupuncture points) had no final placement decision made. Ocker provided the Regence BCBS coverage position on this technology, which is that it is investigational. Ocker and HERC staff will work with acupuncture experts to determine 1) if this HCPCS code is used solely for a device or if it is intended for use for standard electrical stimulation of ear points; 2) if an acupuncturist who does traditional electrical stimulation of ear points can use the usual acupuncture CPT codes for billing; 3) determine if this procedure should be added to any or all of the current lines which contain acupuncture CPT codes. This topic will be readdressed at the January, 2013 VBBS meeting.
- 11) D7952 was added to line 648 (there was a mistake in line number listed in the meeting materials)

Actions:

- 1) See Appendix A for new CPT, CDT and HCPCS code placements
 - a. These proposed placements will be placed on the HERC website to be available for viewing by the various health plans. Final approval of these placements will be done at the HERC meeting on January 10, 2013. These codes will appear on the April 1, 2013 Prioritized List as approved by the HERC in January.
- 2) 77435 was removed from all current lines and are recommended to be added to the Excluded File
- 3) A new guideline was added to line 351 as shown in Appendix B
- 4) 92973, 92975, 92977 were removed from all lines other than lines 51, 76, 108, and 195
- 5) The non-prenatal genetic testing guideline was modified as shown in Appendix C
- 6) Dental guidelines 17 and 53 were modified as shown in Appendix C
- 7) Dental guideline note 91 was deleted

New Discussion Items

➤ **Topic: Silver Nitrate Treatments For Dental Caries**

Discussion: Livingston introduced a summary document regarding use of silver nitrate for treatment of dental caries. Deborah Loy, Capital Dental, submitted written testimony and gave oral testimony against allowing silver nitrate use. She felt that this treatment was not the right treatment for the vulnerable low income population it was targeted for. She testified that its use had no support from professional organizations and had no U.S. evidence to support its use. She feels that its use results in a very poor cosmetic outcome. She also argued that the various types of silver treatment are not interchangeable, and the usual agent used globally is not FDA approved in the US. Loy also acknowledged that if there were good evidence available to support its use, she and others would reconsider, but at this point there is too little known about harms and about comparative efficacy to current treatments.

Dr. Gary Allen a dentist with Advantage Dental, gave written and oral testimony in favor of the use of silver compounds for treatment of dental caries. He testified that the MED review recommendations did not reflect the findings of the review itself. He feels that silver diamine fluoride has evidence of effectiveness, but that this technology is very old and much of the literature would not be found by a standard search of recent studies. He argued that the cosmetic outcome was not that poor, as it turns an otherwise brown stain into a black stain. Silver compounds are used widely internationally to treat dental caries. However, these compounds are not approved in US for this use, but are under review for approval. Silver nitrate + fluoride varnish is being used by some dental providers in Oregon. Silver diamine fluoride would be preferred when available in the US. Dr. Allen argued that silver treatments would be another tool in the toolbox. The typical course of treatment would be 5 applications over a 3-4 month period with restoration at the end of that course. He argued that halting the bacterial infection is important. He also felt that this therapy may be cost savings if avoiding hospitalization of children for extensive dental work.

Tyack asked clarifying questions about the need for further restorative treatment after treatment with silver nitrate. Livingston noted that no studies looked at the comparative outcomes of repeated applications of silver diamide fluoride with delayed restoration vs immediate restoration (what would be standard of care in the United States). Tyack also expressed concern about the potential for discrimination against poor children with black teeth. Glass ionomer cement was offered as another alternative with superior cosmetic outcomes.

Kirk noted that OHP dental director Mike Shirtcliff has reported significant decrease in ER visits with this treatment in his organization.

Livingston also shared public testimony that had been received by Dr. Steven Duffin.

Questions were asked about how silver treatments are billed. The reply was that these treatments are billed with the CDT code for "desensitizing agent" which is not-specific. If the proposed guideline specifying that it is not a covered treatment is not adopted, then dental plans may cover it. Jacobo noted that the desensitizing code is not currently reimbursed by DMAP and would not be reimbursed under FFS, but that the capitated dental plans could choose to reimburse for it.

Tyack expressed concerns for high costs associated with this approach due to mid-level dental providers in FQHC model using this treatment and then billing at the very expensive FQHC wrap-around rate. Allen responded that this would not likely happen under a DCO global budgeting model. Loy replied that even with DCO's, the FQHC wrap-around payment would still apply. Loy noted that the board of dentistry is currently looking into the type of provider that should be allowed to apply silver compounds.

Actions:

The decision was to defer further discussion until the January VBBS meeting. The members will read over the materials in more detail. HERC staff will make a summary of the testimony (written and oral) and other evidence provided for this meeting. HERC staff will also consult the board of dentistry for input on this topic.

➤ Topic: Pseudobulbar Affect

Discussion: Smits introduced a summary document with recommendations regarding the prioritization of pseudobulbar affect (PBA). Testimony was heard from Christina Schad, MD, on behalf of Avanir Pharmaceuticals. She testified that PBA should be a covered condition, as this condition is under-recognized and undertreated. The prevalence of this condition is 10-20% of patients with underlying neurologic conditions and 40% of ALS patients. About 2 million Americans suffer from PBA. PBA causes distress, affects quality of life, and affects occupational functioning. It affects a patient's ability to interact with health care, participate in rehab, and can cause relationship issues. Dr. Schad testified that this condition is a significant burden on patients, family, and caregivers.

Coffman noted that PBA would be covered as a co-morbid condition on the Prioritized List and that the ICD-9 code should be billed as a secondary code when an underlying condition is present.

Pollack noted that he had a patient that he attempted to try this medication for, and had considerable difficulty obtaining coverage for it. He noted that the patient did not respond well to this treatment. He feels that PBA is a significant condition and should be covered.

Smits noted that a new line could be created for PBA with the next biennial review, and scored with the usual methodology. If more timely movement of this condition is needed, the VBBS could consider where such a line would be located and find a similar line in that area of the List that the diagnosis could be added to.

Actions:

No decision was made. Staff will create a mock line with PBA and score it with the usual methodology and bring a proposed new code placement based on this theoretical line to the January VBBS meeting. HERC staff will also contact neurology experts for independent input.

Coverage Guidances for Review**➤ Topic: Viscosupplementation for Osteoarthritis of the Knee**

Discussion: This topic was tabled until the January VBBS meeting.

Actions: Will be discussed at the January VBBS meeting.

➤ **Topic: Percutaneous Interventions for Low Back Pain**

Discussion: This topic was tabled until the January VBBS meeting.

Actions: Will be discussed at the January VBBS meeting.

➤ **Topic: Management of Chronic Otitis Media in Children**

Discussion: Livingston introduced a summary document with recommended changes to the otitis media treatment guideline. Dr. Ericka King from OHSU Pediatric ENT testified about concerns she and her colleagues have about the proposed changes to the guideline and about the literature used for the creation of the HERC coverage guidance on this topic. She recommended re-inserting the stricken language “For the child who has had chronic OME and who has a hearing deficiency in the better-hearing ear of 25 dB or greater, myringotomy with tube insertion recommended after a total of 4 to 6 months of effusion with a documented hearing deficit.” She said that children with a 25dB hearing loss are at risk for language delay.

There was discussion that the current location of chronic OME below the funding line was preventing children from getting needed care. The committee directed Dr. King to bring this concern to the legislature as it is a funding issue.

Livingston brought up that the last sentence regarding individualized treatment plans was problematic for DMAP. She recommended putting in wording that ear tubes should be covered for these diagnoses. There was discussion about adding the CPT code for ear tube to these diagnosis lines (Down’s syndrome, craniofacial anomalies, etc.).

Williams suggested adding PE tubes back to the hearing loss lines. Livingston noted that PE tubes were not indicated for hearing loss unless effusion is present, in which case the diagnosis would be on the chronic OME line.

Actions:

- 1) The chronic otitis media treatment guideline was modified as shown in Appendix C. it will be brought back to the January VBBS meeting as a straightforward item.

Previous Discussion Items

➤ Topic: Puberty Suppression for Transgendered Youth

Discussion: Smits introduced a summary document with information regarding puberty suppression in transgendered youth. Jenn Burleton from TransActive, Dr. Karin Selva from Legacy Pediatric Endocrinology and Dr. Bruce Boston from OHSU Pediatric Endocrinology gave testimony in favor of coverage of this treatment.

The main discussion was about the type of mental health evaluation that would be required prior to this therapy. There are several non-MD mental health providers who are very competent in this area. The proposed guideline wording was changed from “psychiatric evaluation” to “mental health” evaluation.

Tyack and Olson made comments in support of coverage. Tyack felt that there was no alternative treatment and Olson felt that, despite weak evidence, the committee heard strong testimony about the utility of use in this vulnerable population. He also felt that this treatment was unlikely to be abused.

Selva asked that HERC staff ensure that medical visit E&M codes are on the new Gender Dysphoria line for the ICD-10 Prioritized List to allow providers to see these patients for monitoring of this type of treatment. *Note: staff reviewed the new line and it includes E&M codes appropriate for this type of care.*

Actions:

- 1) A new guideline for the gender dysphoria line on the ICD-10 list was adopted as shown in Appendix B

Guidelines

➤ Topic: Guideline note 44, Menstrual Bleeding Disorders

Discussion: Smits introduced a summary document regarding proposed changes to remove a defined hemoglobin level from guideline note 44. Williams expressed concern that without a specific number, there would be no method to objectively determine if anemia was present. Livingston noted that this guideline change would result in increased numbers of hysterectomies for menstrual bleeding disorders. Taray noted that DMAP is already covering many of these cases without the documentation of this hemoglobin level, so the number of new cases with this change would likely be smaller than expected. She noted that there are about 2 cases per month approved by DMAP in the FFS population without a documented hemoglobin of 10. Kirk noted that his plan is using and enforcing this clause. In general, there was a sense that hysterectomy for this indication has significant potential for overuse.

Several alternate wording proposals were put forth. Livingston suggested adding language to require “documented precipitous loss or requiring iron treatment.” Dodson felt that there were already considerable “hoops” to get through in this guideline. She did not feel that the hemoglobin of 10 clause added much to the guideline. She felt that there was no good medical evidence that the value of 10 makes a difference as compared to any other value defining anemia. This number was picked arbitrarily. Taray suggested putting an OR between clauses 1a and 1b; however, the group did not accept this suggestion as it would allow a patient with normal periods but anemia for an unrelated reason to qualify for a hysterectomy.

Actions:

- 1) HERC staff will seek input from the OHP medical directors regarding the utility of having a hemoglobin level of 10 required in this guideline. HERC staff will also research other guidelines, such as Blue Cross, to see what type of definition is used for anemia, if any. This topic will be brought back to the March 2013 VBBS meeting (the next OHP medical directors meeting is after the January VBBS meeting)

➤ **Topic: Prenatal genetic testing guideline**

Discussion: Livingston introduced a summary document regarding plans to create a prenatal genetic testing guideline. The group decided that it should go through the coverage guidance process and engaging experts to assist.

Actions:

- 1) HERC staff to identify experts and bring to a subsequent Evidence-based Guidelines Subcommittee meeting

➤ **Public Comment:**

No additional public comment was received

➤ **Issues for next meeting:**

- Coronary brachytherapy
- External elements exposure issues
- Stereotactic radiation therapy for intracranial AVMs (
- Personal history of cancer V codes
- Auricular acupuncture
- Enzyme replacement therapy for Guacher’s disease and PKU
- Silver compounds for caries treatment
- Pseudobulbar affect prioritization
- Changes needed to the Prioritized List to bring into alignment with coverage guidances on viscosupplementation for osteoarthritis of the knee, percutaneous

interventions for low back pain, and management of chronic otitis media in children

- Guideline on immunizations/prevention tables
- Expensive/marginally effective drug guideline
- Guideline Note 37 on abnormal reflexes radiculopathy

➤ **Next meeting:**

Thursday, January 10, 2013, Meridian Park Hospital, Conference Room 117
Time: TBD

The meeting adjourned at 2:45 PM.

DRAFT

Appendix A

Recommended Placement of New 2013 CPT, CDT and HCPCS Codes

DRAFT

2012 CPT Code Review

Code	Code Description	List/File	Proposed April 2013 Placement	Notes
22586	Arthrodesis, anterior interbody technique, including minimal discectomy to prepare interspace (other than for decompression); each additional interspace	Prioritized	84 DEEP ABSCESSSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS; INTESTINAL PERFORATION 158 CERVICAL VERTEBRAL DISLOCATIONS/FRACTURES, OPEN OR CLOSED; OTHER VERTEBRAL DISLOCATIONS/FRACTURES, OPEN; SPINAL CORD INJURIES WITH OR WITHOUT EVIDENCE OF VERTEBRAL INJURY 208 CANCER OF BONES 271 CHRONIC OSTEOMYELITIS 400 DISORDERS OF SPINE WITH NEUROLOGIC IMPAIRMENT 434 SPINAL DEFORMITY, CLINICALLY SIGNIFICANT 507 CLOSED DISLOCATIONS/FRACTURES OF NON-CERVICAL VERTEBRAL COLUMN WITHOUT SPINAL CORD INJURY 549 BENIGN NEOPLASM BONE AND ARTICULAR CARTILAGE INCLUDING OSTEOID OSTEOMAS; BENIGN NEOPLASM OF CONNECTIVE AND OTHER SOFT TISSUE 607 SPINAL DEFORMITY, NOT CLINICALLY SIGNIFICANT	
23473	Revision of total shoulder arthroplasty, including allograft when performed; humeral or glenoid component	Prioritized	208 CANCER OF BONES 308 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 384 RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, OSTEOCHONDRITIS DISSECANS, AND ASEPTIC NECROSIS OF BONE 467 MALUNION AND NONUNION OF FRACTURE	
23474	Revision of total shoulder arthroplasty, including allograft when performed; humeral and glenoid component	Prioritized	208 CANCER OF BONES 308 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 384 RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, OSTEOCHONDRITIS DISSECANS, AND ASEPTIC NECROSIS OF BONE 467 MALUNION AND NONUNION OF FRACTURE	
24370	Revision of total elbow arthroplasty, including allograft when performed; humeral or ulnar component	Prioritized	208 CANCER OF BONES 384 RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, OSTEOCHONDRITIS DISSECANS, AND ASEPTIC NECROSIS OF BONE	
24371	Revision of total elbow arthroplasty, including allograft when performed; humeral and ulnar component	Prioritized	208 CANCER OF BONES 384 RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, OSTEOCHONDRITIS DISSECANS, AND ASEPTIC NECROSIS OF BONE	
31647	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with balloon occlusion, when performed, assessment of air leak, airway sizing, and insertion of bronchial valve(s), initial lobe	Excluded		
31648	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with removal of bronchial valve(s), initial lobe	Excluded		
31649	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with removal of bronchial valve(s), each additional lobe	Excluded		

2012 CPT Code Review

Code	Code Description	List/File	Proposed April 2013 Placement	Notes
31651	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with balloon occlusion, when performed, assessment of air leak, airway sizing, and insertion of bronchial valve(s), each additional lobe	Excluded		
31660	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with bronchial thermoplasty, 1 lobe	Excluded		
31661	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with bronchial thermoplasty, 2 or more lobes	Excluded		
32554	Thoracentesis, needle or catheter, aspiration of the pleural space; without imaging guidance	Prioritized	84 DEEP ABSCESSSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS; INTESTINAL PERFORATION 153 PNEUMOTHORAX AND HEMOTHORAX	
32555	with imaging guidance	Prioritized	84 DEEP ABSCESSSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS; INTESTINAL PERFORATION 153 PNEUMOTHORAX AND HEMOTHORAX	
32556	Pleural drainage, percutaneous, with insertion of indwelling catheter; without imaging guidance	Prioritized	84 DEEP ABSCESSSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS; INTESTINAL PERFORATION 153 PNEUMOTHORAX AND HEMOTHORAX	
32557	with imaging guidance	Prioritized	84 DEEP ABSCESSSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS; INTESTINAL PERFORATION 153 PNEUMOTHORAX AND HEMOTHORAX	
32701	Thoracic target(s) delineation for stereotactic body radiation therapy (SRS/SBRT), (photon or particle beam), entire course of treatment	Excluded		
33361	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; percutaneous femoral artery approach	Prioritized	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, HISTOPLASMOSES, BLASTOMYCOTIC INFECTION, OPPORTUNISTIC AND OTHER MYCOSES	
33362	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open femoral artery approach	Prioritized	76, 90, 116, 192, 195, 237, 308, 354	
33363	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open axillary artery approach	Prioritized	76, 90, 116, 192, 195, 237, 308, 354	
33364	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open iliac artery approach	Prioritized	76, 90, 116, 192, 195, 237, 308, 354	

2012 CPT Code Review

Code	Code Description	List/File	Proposed April 2013 Placement	Notes
33365	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; transaortic approach (eg, median sternotomy, mediastinotomy)	Prioritized	76, 90, 116, 192, 195, 237, 308, 354	
33367	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; cardiopulmonary bypass support with percutaneous peripheral arterial and venous cannulation (eg, femoral vessels) (List separately in addition to code for primary procedure)	Prioritized	76, 90, 116, 192, 195, 237, 308, 354	
33368	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; cardiopulmonary bypass support with open peripheral arterial and venous cannulation (eg, femoral, iliac, axillary vessels) (List separately in addition to code for primary procedure)	Prioritized	76, 90, 116, 192, 195, 237, 308, 354	
33369	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; cardiopulmonary bypass support with central arterial and venous cannulation (eg, aorta, right atrium, pulmonary artery) (List separately in addition to code for primary procedure)	Prioritized	76, 90, 116, 192, 195, 237, 308, 354	
33990	Insertion of ventricular assist device, percutaneous including radiological supervision and interpretation; arterial access only	Prioritized	90 MYOCARDITIS (NONVIRAL), PERICARDITIS (NONVIRAL) AND ENDOCARDITIS 108 HEART FAILURE 279 CONGESTIVE HEART FAILURE, CARDIOMYOPATHY, TRANSPOSITION OF GREAT VESSELS, HYPOPLASTIC LEFT HEART SYNDROME 367 IDIOPATHIC OR VIRAL MYOCARDITIS AND PERICARDITIS	
33991	Insertion of ventricular assist device, percutaneous including radiological supervision and interpretation; both arterial and venous access, with transseptal puncture	Prioritized	90, 108, 279, 367	
33992	Removal of percutaneous ventricular assist device at separate and distinct session from insertion	Prioritized	90, 108, 279, 367	
33993	Repositioning of percutaneous ventricular assist device with imaging guidance at separate and distinct session from insertion	Prioritized	90, 108, 279, 367	

Code	Code Description	List/File	Proposed April 2013 Placement	Notes
36221	Non-selective catheter placement, thoracic aorta, with angiography of the extracranial carotid, vertebral, and/or intracranial vessels, unilateral or bilateral, and all associated radiological supervision and interpretation, includes angiography of the cervicocerebral arch, when performed	Diagnostic		
36222	Selective catheter placement, common carotid or innominate artery, unilateral, any approach, with angiography of the ipsilateral extracranial carotid circulation and all associated radiological supervision and interpretation, includes angiography of the extracranial carotid and cervicocerebral arch, when performed	Diagnostic		
36223	Selective catheter placement, common carotid or innominate artery, unilateral, any approach, with angiography of the ipsilateral intracranial carotid circulation and all associated radiological supervision and interpretation, includes angiography of the extracranial carotid and cervicocerebral arch, when performed	Diagnostic		
36224	Selective catheter placement, internal carotid artery, unilateral, with angiography of the ipsilateral intracranial carotid circulation and all associated radiological supervision and interpretation, includes angiography of the extracranial carotid and cervicocerebral arch, when performed	Diagnostic		
36225	Selective catheter placement, subclavian or innominate artery, unilateral, with angiography of the ipsilateral vertebral circulation and all associated radiological supervision and interpretation, includes angiography of the cervicocerebral arch, when performed	Diagnostic		
36226	Selective catheter placement, vertebral artery, unilateral, with angiography of the ipsilateral vertebral circulation and all associated radiological supervision and interpretation, includes angiography of the cervicocerebral arch, when performed	Diagnostic		

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Code	Code Description	List/File	Proposed April 2013 Placement	Notes
36227	Selective catheter placement, external carotid artery, unilateral, with angiography of the ipsilateral external carotid circulation and all associated radiological supervision and interpretation	Diagnostic		
36228	Selective catheter placement, each intracranial branch of the internal carotid or vertebral arteries, unilateral, with angiography of the selected vessel circulation and all associated radiological supervision and interpretation (eg, middle cerebral artery, posterior inferior cerebellar artery)	Diagnostic		
37197	Transcatheter retrieval, percutaneous, of intravascular foreign body (eg, fractured venous or arterial catheter), includes radiological supervision and interpretation, and imaging guidance (ultrasound or fluoroscopy), when performed	Prioritized	308 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT	
37211	Transcatheter therapy, arterial infusion for thrombolysis other than coronary, any method, including radiological supervision and interpretation, initial treatment day	Prioritized	270 ARTERIAL EMBOLISM/THROMBOSIS: ABDOMINAL AORTA, THORACIC AORTA 342 STROKE 378 ATHEROSCLEROSIS, PERIPHERAL 472 ATHEROSCLEROSIS, AORTIC AND RENAL	
37212	Transcatheter therapy, venous infusion for thrombolysis, any method, including radiological supervision and interpretation, initial treatment day	Prioritized	87 PHLEBITIS AND THROMBOPHLEBITIS, DEEP 303 BUDD-CHIARI SYNDROME, AND OTHER VENOUS EMBOLISM AND THROMBOSIS	
37213	Transcatheter therapy, arterial or venous infusion for thrombolysis other than coronary, any method, including radiological supervision and interpretation, continued treatment on subsequent day during course of thrombolytic therapy, including follow-up catheter contrast injection, position change, or exchange, when performed;	Prioritized	87 PHLEBITIS AND THROMBOPHLEBITIS, DEEP 270 ARTERIAL EMBOLISM/THROMBOSIS: ABDOMINAL AORTA, THORACIC AORTA 303 BUDD-CHIARI SYNDROME, AND OTHER VENOUS EMBOLISM AND THROMBOSIS 342 STROKE 378 ATHEROSCLEROSIS, PERIPHERAL 472 ATHEROSCLEROSIS, AORTIC AND RENAL	

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Code	Code Description	List/File	Proposed April 2013 Placement	Notes
37214	Transcatheter therapy, arterial or venous infusion for thrombolysis other than coronary, any method, including radiological supervision and interpretation, continued treatment on subsequent day during course of thrombolytic therapy, including follow-up catheter contrast injection, position change, or exchange, when performed; cessation of thrombolysis including removal of catheter and vessel closure by any method	Prioritized	87 PHLEBITIS AND THROMBOPHLEBITIS, DEEP 270 ARTERIAL EMBOLISM/THROMBOSIS: ABDOMINAL AORTA, THORACIC AORTA 303 BUDD-CHIARI SYNDROME, AND OTHER VENOUS EMBOLISM AND THROMBOSIS 342 STROKE 378 ATHEROSCLEROSIS, PERIPHERAL 472 ATHEROSCLEROSIS, AORTIC AND RENAL	
38243	Hematopoietic progenitor cell (HPC); HPC boost	Prioritized	79 AGRANULOCYTOSIS 103 ACUTE LEUKEMIAS, MYELOYDPLASTIC SYNDROME 105 HEREDITARY IMMUNE DEFICIENCIES 125 HODGKIN'S DISEASE 131 OTHER SPECIFIED APLASTIC ANEMIAS 170 NON-HODGKIN'S LYMPHOMAS 198 MULTIPLE MYELOMA 206 CONSTITUTIONAL APLASTIC ANEMIAS 231 TESTICULAR CANCER 280 CHRONIC NON-LYMPHOCYTIC LEUKEMIA 314 OSTEOPETROSIS	
43206	Esophagoscopy, rigid or flexible; with optical endomicroscopy	Excluded		
43252	Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; with optical endomicroscopy	Excluded		
44705	Preparation of fecal microbiota for instillation, including assessment of donor specimen	Excluded		
52287	Cystourethroscopy, with injection(s) for chemodenervation of the bladder	Prioritized	351 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION	
64615	Chemodenervation of muscle(s); muscle(s) innervated by facial, trigeminal, cervical spinal and accessory nerves, bilateral (eg, for chronic migraine)	Excluded		
78012	Thyroid uptake, single or multiple quantitative measurement(s) (including stimulation, suppression, or discharge, when performed)	Diagnostic		
78013	Thyroid imaging (including vascular flow, when performed);	Diagnostic		

Code	Code Description	List/File	Proposed April 2013 Placement	Notes
78014	Thyroid imaging (including vascular flow, when performed); with single or multiple uptake(s) quantitative measurement(s) (including stimulation, suppression, or discharge, when performed)	Diagnostic		
78071	Parathyroid planar imaging (including subtraction, when performed); with tomographic (SPECT)	Diagnostic		
78072	Parathyroid planar imaging (including subtraction, when performed); with tomographic (SPECT), and concurrently acquired computed tomography (CT) for anatomical localization	Diagnostic		
81201	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence	Diagnostic		
81202	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants	Diagnostic		
81203	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants	Diagnostic		
81235	EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)	Prioritized	278 CANCER OF LUNG, BRONCHUS, PLEURA, TRACHEA, MEDIASTINUM AND OTHER RESPIRATORY ORGANS	
81252	GJB2 (gap junction protein, beta 2, 26kDa; connexin 26) (eg, nonsyndromic hearing loss) gene analysis; full gene sequence	Diagnostic		
81253	GJB2 (gap junction protein, beta 2, 26kDa; connexin 26) (eg, nonsyndromic hearing loss) gene analysis; known familial variants	Diagnostic		
81254	GJB6 (gap junction protein, beta 6, 30kDa, connexin 30) (eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])	Diagnostic		

Code	Code Description	List/File	Proposed April 2013 Placement	Notes
81321	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis	Diagnostic		
81322	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant	Diagnostic		
81323	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant	Diagnostic		
81324	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis	Diagnostic		
81325	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis	Diagnostic		
81326	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; known familial variant	Diagnostic		
81479	Unlisted molecular pathology procedure	Suspend for Review		
81500	Oncology (ovarian), biochemical assays of two proteins (CA-125 and HE4), utilizing serum, with menopausal status, algorithm reported as a risk score	Excluded		
81503	Oncology (ovarian), biochemical assays of five proteins (CA-125, apolipoprotein A1, beta-2 microglobulin, transferrin, and pre-albumin), utilizing serum, algorithm reported as a risk score	Excluded		
81506	Endocrinology (type 2 diabetes), biochemical assays of seven analytes (glucose, HbA1c, insulin, hs-CRP, adiponectin, ferritin, interleukin 2-receptor alpha), utilizing serum or plasma, algorithm reporting a risk score	Excluded		

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Code	Code Description	List/File	Proposed April 2013 Placement	Notes
81508	Fetal congenital abnormalities, biochemical assays of two proteins (PAPP-A, hCG [any form]), utilizing maternal serum, algorithm reported as a risk score	Prioritized	1 PREGNANCY	
81509	Fetal congenital abnormalities, biochemical assays of three proteins (PAPP-A, hCG [any form], DIA), utilizing maternal serum, algorithm reported as a risk score	Prioritized	1 PREGNANCY	
81510	Fetal congenital abnormalities, biochemical assays of three analytes (AFP, uE3, hCG [any form]), utilizing maternal serum, algorithm reported as a risk score	Prioritized	1 PREGNANCY	
81511	Fetal congenital abnormalities, biochemical assays of four analytes (AFP, uE3, hCG [any form], DIA) utilizing maternal serum, algorithm reported as a risk score (may include additional results from previous biochemical testing)	Prioritized	1 PREGNANCY	
81512	Fetal congenital abnormalities, biochemical assays of five analytes (AFP, uE3, total hCG, hyperglycosylated hCG, DIA) utilizing maternal serum, algorithm reported as a risk score	Prioritized	1 PREGNANCY	
81599	Unlisted multianalyte assay with algorithmic analysis	Suspend for Review		
82777	Galectin-3	Excluded		
86152	Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood)	Excluded		
86153	Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood); physician interpretation and report, when required	Excluded		
86711	Antibody; JC (John Cunningham) virus	Diagnostic	35 REGIONAL ENTERITIS, IDIOPATHIC PROCTOCOLITIS, ULCERATION OF INTESTINE 268 MULTIPLE SCLEROSIS AND OTHER DEMYELINATING DISEASES OF CENTRAL NERVOUS SYSTEM	

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Code	Code Description	List/File	Proposed April 2013 Placement	Notes
86828	Antibody to human leukocyte antigens (HLA), solid phase assays (eg, microspheres or beads, ELISA, flow cytometry); qualitative assessment of the presence or absence of antibody(ies) to HLA Class I and Class II HLA antigens	Prioritized	Transplant lines (78, 92, 103, 105, 110, 125, 131, 169, 170, 198, 206, 232, 253, 254, 255, 279, 280, 314, 333, 574)	
86829	Antibody to human leukocyte antigens (HLA), solid phase assays (eg, microspheres or beads, ELISA, Flow cytometry); qualitative assessment of the presence or absence of antibody(ies) to HLA Class I or Class II HLA antigens	Prioritized	Transplant lines (78, 92, 103, 105, 110, 125, 131, 169, 170, 198, 206, 232, 253, 254, 255, 279, 280, 314, 333, 574)	
86830	Antibody to human leukocyte antigens (HLA), solid phase assays (eg, microspheres or beads, ELISA, Flow cytometry); antibody identification by qualitative panel using complete HLA phenotypes, HLA Class I	Prioritized	Transplant lines (78, 92, 103, 105, 110, 125, 131, 169, 170, 198, 206, 232, 253, 254, 255, 279, 280, 314, 333, 574)	
86831	Antibody to human leukocyte antigens (HLA), solid phase assays (eg, microspheres or beads, ELISA, Flow cytometry); antibody identification by qualitative panel using complete HLA phenotypes, HLA Class II	Prioritized	Transplant lines (78, 92, 103, 105, 110, 125, 131, 169, 170, 198, 206, 232, 253, 254, 255, 279, 280, 314, 333, 574)	
86832	Antibody to human leukocyte antigens (HLA), solid phase assays (eg, microspheres or beads, ELISA, Flow cytometry); high definition qualitative panel for identification of antibody specificities (eg, individual antigen per bead methodology), HLA Class I	Prioritized	Transplant lines (78, 92, 103, 105, 110, 125, 131, 169, 170, 198, 206, 232, 253, 254, 255, 279, 280, 314, 333, 574)	
86833	Antibody to human leukocyte antigens (HLA), solid phase assays (eg, microspheres or beads, ELISA, Flow cytometry); high definition qualitative panel for identification of antibody specificities (eg, individual antigen per bead methodology), HLA Class II	Prioritized	Transplant lines (78, 92, 103, 105, 110, 125, 131, 169, 170, 198, 206, 232, 253, 254, 255, 279, 280, 314, 333, 574)	
86834	Antibody to human leukocyte antigens (HLA), solid phase assays (eg, microspheres or beads, ELISA, Flow cytometry); semi-quantitative panel (eg, titer), HLA Class I	Prioritized	Transplant lines (78, 92, 103, 105, 110, 125, 131, 169, 170, 198, 206, 232, 253, 254, 255, 279, 280, 314, 333, 574)	
86835	Antibody to human leukocyte antigens (HLA), solid phase assays (eg, microspheres or beads, ELISA, Flow cytometry); semi-quantitative panel (eg, titer), HLA Class II	Prioritized	Transplant lines (78, 92, 103, 105, 110, 125, 131, 169, 170, 198, 206, 232, 253, 254, 255, 279, 280, 314, 333, 574)	

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Code	Code Description	List/File	Proposed April 2013 Placement	Notes
87631	Infectious agent detection by nucleic acid (DNA or RNA); respiratory virus (eg, adenovirus, influenza virus, coronavirus, metapneumovirus, parainfluenza virus, respiratory syncytial virus, rhinovirus), multiplex reverse transcription and amplified probe technique, multiple types or subtypes, 3-5 targets	Diagnostic		
87632	6-11 targets	Diagnostic		
87633	12-25 targets	Diagnostic		
87910	Infectious agent genotype analysis by nucleic acid (DNA or RNA); cytomegalovirus	Diagnostic		
87912	Infectious agent genotype analysis by nucleic acid (DNA or RNA); Hepatitis B virus	Diagnostic		
88375	Optical endomicroscopic image(s), interpretation and report, real-time or referred, each endoscopic session	Excluded		
90653	Influenza vaccine, inactivated, subunit, adjuvanted, for intramuscular use	Prioritized	3 PREVENTIVE SERVICES, BIRTH TO 10 YEARS OF AGE 4 PREVENTIVE SERVICES, OVER AGE OF 10	
90672	Influenza virus vaccine, quadrivalent, live, for intranasal use	Prioritized	3 PREVENTIVE SERVICES, BIRTH TO 10 YEARS OF AGE 4 PREVENTIVE SERVICES, OVER AGE OF 10	
90739	Hepatitis B vaccine, adult dosage (2 dose schedule), for intramuscular use	Prioritized	4 PREVENTIVE SERVICES, OVER AGE OF 10	
90785	Interactive complexity (List separately in addition to the code for primary procedure)	Prioritized	MHCD Lines (5,9,27,32,68,70,107,133,180,209,212,222,269,295,305,316,334,390,398,400,412,417,419,425,431,437,445,457,462,469,471,474,481,483,487,488,496,500,508,518,521,544,546,562,569,576,588,608,609,660)	
90791	Psychiatric diagnostic evaluation	Diagnostic		
90792	Psychiatric diagnostic evaluation with medical services	Diagnostic		
90832	Psychotherapy, 30 minutes with patient and/or family member	Prioritized	MHCD Lines (see 90785)	
90833	Psychotherapy, 30 minutes with patient and/or family member when performed with an evaluation and management service	Prioritized	MHCD Lines (see 90785)	
90834	Psychotherapy, 45 minutes with patient and/or family member	Prioritized	MHCD Lines (see 90785)	
90836	Psychotherapy, 45 minutes with patient and/or family member when performed with an evaluation and management service	Prioritized	MHCD Lines (see 90785)	
90837	Psychotherapy, 60 minutes with patient and/or family member	Prioritized	MHCD Lines (see 90785)	

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Code	Code Description	List/File	Proposed April 2013 Placement	Notes
90838	Psychotherapy, 60 minutes with patient and/or family member when performed with an evaluation and management service	Prioritized	MHCD Lines (see 90785)	
90839	Psychotherapy for crisis; first 60 minutes	Prioritized	MHCD Lines (see 90785)	
90840	Psychotherapy for crisis; each additional 30 minutes	Prioritized	MHCD Lines (see 90785)	
90863	Pharmacologic management, including prescription and review of medication, when performed with psychotherapy services	Excluded		
91112	Gastrointestinal transit and pressure measurement, stomach through colon, wireless capsule, with interpretation and report	Excluded		
92920	Percutaneous transluminal coronary angioplasty; single major coronary artery or branch	Prioritized	51 CORONARY ARTERY ANOMALY 76 ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION 108 HEART FAILURE 195 CHRONIC ISCHEMIC HEART DISEASE	
92921	each additional branch of a major coronary artery	Prioritized	51 CORONARY ARTERY ANOMALY 76 ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION 108 HEART FAILURE 195 CHRONIC ISCHEMIC HEART DISEASE	
92924	Percutaneous transluminal coronary atherectomy, with coronary angioplasty when performed; single major coronary artery or branch	Prioritized	51 CORONARY ARTERY ANOMALY 76 ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION 108 HEART FAILURE 195 CHRONIC ISCHEMIC HEART DISEASE	
92925	each additional branch of a major coronary artery	Prioritized	51 CORONARY ARTERY ANOMALY 76 ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION 108 HEART FAILURE 195 CHRONIC ISCHEMIC HEART DISEASE	
92928	Percutaneous transcatheter placement of intracoronary stent(s), with coronary angioplasty when performed; single major coronary artery or branch	Prioritized	51 CORONARY ARTERY ANOMALY 76 ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION 108 HEART FAILURE 195 CHRONIC ISCHEMIC HEART DISEASE	
92929	each additional branch of a major coronary artery	Prioritized	51 CORONARY ARTERY ANOMALY 76 ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION 108 HEART FAILURE 195 CHRONIC ISCHEMIC HEART DISEASE	
92933	Percutaneous transluminal coronary atherectomy, with intracoronary stent, with coronary angioplasty when performed; single major coronary artery or branch	Prioritized	51 CORONARY ARTERY ANOMALY 76 ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION 108 HEART FAILURE 195 CHRONIC ISCHEMIC HEART DISEASE	

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Code	Code Description	List/File	Proposed April 2013 Placement	Notes
92934	each additional branch of a major coronary artery	Prioritized	51 CORONARY ARTERY ANOMALY 76 ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION 108 HEART FAILURE 195 CHRONIC ISCHEMIC HEART DISEASE	
92937	Percutaneous transluminal revascularization of or through coronary artery bypass graft (internal mammary, free arterial, venous), any combination of intracoronary stent, atherectomy and angioplasty, including distal protection when performed; single vessel	Prioritized	51 CORONARY ARTERY ANOMALY 76 ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION 108 HEART FAILURE 195 CHRONIC ISCHEMIC HEART DISEASE	
92938	each additional branch subtended by the bypass graft	Prioritized	51 CORONARY ARTERY ANOMALY 76 ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION 108 HEART FAILURE 195 CHRONIC ISCHEMIC HEART DISEASE	
92941	Percutaneous transluminal revascularization of acute total/subtotal occlusion during acute myocardial infarction, coronary artery or coronary artery bypass graft, any combination of intracoronary stent, atherectomy and angioplasty, including aspiration thrombectomy when performed, single vessel	Prioritized	76 ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION	
92943	Percutaneous transluminal revascularization of chronic total occlusion, coronary artery, coronary artery branch, or coronary artery bypass graft, any combination of intracoronary stent, atherectomy and angioplasty; single vessel	Prioritized	51 CORONARY ARTERY ANOMALY 76 ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION 108 HEART FAILURE 195 CHRONIC ISCHEMIC HEART DISEASE	
92944	each additional coronary artery, coronary artery branch, or bypass graft	Prioritized	51 CORONARY ARTERY ANOMALY 76 ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION 108 HEART FAILURE 195 CHRONIC ISCHEMIC HEART DISEASE	

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Code	Code Description	List/File	Proposed April 2013 Placement	Notes
93653	Comprehensive electrophysiologic evaluation including insertion and repositioning of multiple electrode catheters with induction or attempted induction of an arrhythmia with right atrial pacing and recording, right ventricular pacing and recording, His recording with intracardiac catheter ablation of arrhythmogenic focus; with treatment of supraventricular tachycardia by ablation of fast or slow atrioventricular pathway, accessory atrioventricular connection, cavo-tricuspid isthmus or other single atrial focus or source of atrial re-entry	Prioritized	304 LIFE-THREATENING CARDIAC ARRHYTHMIAS 376 CARDIAC ARRHYTHMIAS	
93654	Comprehensive electrophysiologic evaluation including insertion and repositioning of multiple electrode catheters with induction or attempted induction of an arrhythmia with right atrial pacing and recording, right ventricular pacing and recording, His recording with intracardiac catheter ablation of arrhythmogenic focus; with treatment of ventricular tachycardia or focus of ventricular ectopy including intracardiac electrophysiologic 3D mapping, when performed, and left ventricular pacing and recording, when performed	Prioritized	304 LIFE-THREATENING CARDIAC ARRHYTHMIAS 376 CARDIAC ARRHYTHMIAS	
93655	Intracardiac catheter ablation of a discrete mechanism of arrhythmia which is distinct from the primary ablated mechanism, including repeat diagnostic maneuvers, to treat a spontaneous or induced arrhythmia	Prioritized	304 LIFE-THREATENING CARDIAC ARRHYTHMIAS 376 CARDIAC ARRHYTHMIAS	
93656	Comprehensive electrophysiologic evaluation including transseptal catheterizations, insertion and repositioning of multiple electrode catheters with induction or attempted induction of an arrhythmia with atrial recording and pacing, when possible, right ventricular pacing and recording, His bundle recording with intracardiac catheter ablation of arrhythmogenic focus, with treatment of atrial fibrillation by ablation by pulmonary vein isolation	Prioritized	304 LIFE-THREATENING CARDIAC ARRHYTHMIAS 376 CARDIAC ARRHYTHMIAS	

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Code	Code Description	List/File	Proposed April 2013 Placement	Notes
93657	Additional linear or focal intracardiac catheter ablation of the left or right atrium for treatment of atrial fibrillation remaining after completion of pulmonary vein isolation	Prioritized	376 CARDIAC ARRHYTHMIAS	
95017	Allergy testing, any combination of percutaneous (scratch, puncture, prick) and intracutaneous (intradermal), sequential and incremental, with venoms, immediate type reaction, including test interpretation and report, specify number of tests	Prioritized	113 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS 234 ANAPHYLACTIC SHOCK; EDEMA OF LARYNX	
95018	Allergy testing, any combination of percutaneous (scratch, puncture, prick) and intracutaneous (intradermal), sequential and incremental, with drugs or biologicals, immediate type reaction, including test interpretation and report, specify number of tests	Prioritized	11 ASTHMA 113 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS 234 ANAPHYLACTIC SHOCK; EDEMA OF LARYNX 236 OCCUPATIONAL LUNG DISEASES 338 DISORDERS INVOLVING THE IMMUNE SYSTEM 553 ATOPIC DERMATITIS 554 CONTACT DERMATITIS AND OTHER ECZEMA 575 OTHER NONINFECTIOUS GASTROENTERITIS AND COLITIS 585 ALLERGIC RHINITIS AND CONJUNCTIVITIS, CHRONIC RHINITIS 594 DERMATITIS DUE TO SUBSTANCES TAKEN INTERNALLY	
95076	Ingestion challenge test (sequential and incremental ingestion of test items, eg, food, drug or other substance); initial 120 minutes of testing	Prioritized	11 ASTHMA 113 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS 234 ANAPHYLACTIC SHOCK; EDEMA OF LARYNX 236 OCCUPATIONAL LUNG DISEASES 338 DISORDERS INVOLVING THE IMMUNE SYSTEM 553 ATOPIC DERMATITIS 554 CONTACT DERMATITIS AND OTHER ECZEMA 575 OTHER NONINFECTIOUS GASTROENTERITIS AND COLITIS 585 ALLERGIC RHINITIS AND CONJUNCTIVITIS, CHRONIC RHINITIS 594 DERMATITIS DUE TO SUBSTANCES TAKEN INTERNALLY	
95079	each additional 60 minutes of testing	Prioritized	11 ASTHMA 113 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS 234 ANAPHYLACTIC SHOCK; EDEMA OF LARYNX 236 OCCUPATIONAL LUNG DISEASES 338 DISORDERS INVOLVING THE IMMUNE SYSTEM 553 ATOPIC DERMATITIS 554 CONTACT DERMATITIS AND OTHER ECZEMA 575 OTHER NONINFECTIOUS GASTROENTERITIS AND COLITIS 585 ALLERGIC RHINITIS AND CONJUNCTIVITIS, CHRONIC RHINITIS 594 DERMATITIS DUE TO SUBSTANCES TAKEN INTERNALLY	
95782	Polysomnography; younger than 6 years, sleep staging with 4 or more additional parameters of sleep, attended by a technologist	Diagnostic		

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Code	Code Description	List/File	Proposed April 2013 Placement	Notes
95783	Polysomnography; younger than 6 years, sleep staging with 4 or more additional parameters of sleep, with initiation of continuous positive airway pressure therapy or bi-level ventilation, attended by a technologist	Diagnostic		
95907	Nerve conduction studies; 1-2 studies	Diagnostic		
95908	Nerve conduction studies; 3-4 studies	Diagnostic		
95909	Nerve conduction studies; 5-6 studies	Diagnostic		
95910	Nerve conduction studies; 7-8 studies	Diagnostic		
95911	Nerve conduction studies; 9-10 studies	Diagnostic		
95912	Nerve conduction studies; 11-12 studies	Diagnostic		
95913	Nerve conduction studies; 13 or more studies	Diagnostic		
95924	Testing of autonomic nervous system function; combined parasympathetic and sympathetic adrenergic function testing with at least 5 minutes of passive tilt	Diagnostic		
95940	Continuous intraoperative neurophysiology monitoring in the operating room, one on one monitoring requiring personal attendance, each 15 minutes	Ancillary		
95941	Continuous intraoperative neurophysiology monitoring, from outside the operating room (remote or nearby) or for monitoring of more than one case while in the operating room, per hour	Ancillary		
95943	Simultaneous, independent, quantitative measures of both parasympathetic function and sympathetic function, based on time-frequency analysis of heart rate variability concurrent with time-frequency analysis of continuous respiratory activity, with mean heart rate and blood pressure measures, during rest, paced (deep) breathing, Valsalva maneuvers, and head-up postural change	Diagnostic		

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Code	Code Description	List/File	Proposed April 2013 Placement	Notes
99485	Supervision by a control physician of interfacility transport care of the critically ill or critically injured pediatric patient, 24 months of age or younger, includes two-way communication with transport team before transport, at the referring facility and during the transport, including data interpretation and report; first 30 minutes	Exempt		
99486	each additional 30 minutes	Exempt		
99487	Complex chronic care coordination services; first hour of clinical staff time directed by a physician or other qualified health care professional with no face-to-face visit, per calendar month	Prioritized	*E&M Lines (See below, final page)	
99488	Complex chronic care coordination services; first hour of clinical staff time directed by a physician or other qualified health care professional with one face-to-face visit, per calendar month	Prioritized	*E&M Lines (See below, final page)	
99489	Complex chronic care coordination services; each additional 30 minutes of clinical staff time directed by a physician or other qualified health care professional, per calendar month	Prioritized	*E&M Lines (See below, final page)	
99495	Transitional Care Management Services with the following required elements: Communication (direct contact, telephone, electronic) with the patient and/or caregiver within 2 business days of discharge Medical decision making of at least moderate complexity during the service period Face-to-face visit, within 14 calendar days of discharge	Prioritized	*E&M Lines (See below, final page)	
99496	Transitional Care Management Services with the following required elements: Communication (direct contact, telephone, electronic) with the patient and/or caregiver within 2 business days of discharge Medical decision making of high complexity during the service period Face-to-face visit, within 7 calendar days of discharge	Prioritized	*E&M Lines (See below, final page)	

2012 CPT Code Review

Code	Code Description	List/File	Proposed April 2013 Placement	Notes
HCPCS Code				
G0452	Molecular pathology procedure; physician interpretation and report	Suspend for Review		
G0453	Continuous intraoperative neurophysiology monitoring, from outside the operating room (remote or nearby), per patient, (attention directed exclusively to one patient) each 15 minutes (list in addition to primary procedure)	Ancillary		
G0454	Physician documentation of face-to-face visit for durable medical equipment determination performed by nurse practitioner, physician assistant or clinical nurse specialist	Ancillary		
G0455	Preparation with instillation of fecal microbiota by any method, including assessment of donor specimen	Excluded		
G0456	Negative pressure wound therapy, (e. G. Vacuum assisted drainage collection) using a mechanically-powered device, not durable medical equipment, including provision of cartridge and dressing(s), topical application(s), wound assessment, and instructions f	Ancillary		
G0457	Negative pressure wound therapy, (e. G. Vacuum assisted drainage collection) using a mechanically-powered device, not durable medical equipment, including provision of cartridge and dressing(s), topical application(s), wound assessment, and instructions f	Ancillary		
G0458	Low dose rate (ldr) prostate brachytherapy services, composite rate	Prioritized	356 CANCER OF PROSTATE GLAND	
S0353	Treatment planning and care coordination management for cancer, initial treatment	Ancillary		
S0354	Treatment planning and care coordination management for cancer, established patient with a change of regimen	Ancillary		
S3721	Prostate cancer antigen 3 (pca3) testing	Excluded		
S8930	Electrical stimulation of auricular acupuncture points; each 15 minutes of personal one-on-one contact with the patient		No decision made. Will review at the January, 2013 VBBS meeting	

Code	Code Description	List/File	Proposed April 2013 Placement	Notes
CDT Codes				
D0190	Screening of a patient - a screening, including state or federally mandated screenings, to determine an individual's need to be seen by a dentist for diagnosis.	Excluded		
D0191	Assessment of a patient - a limited clinical inspection that is performed to identify possible signs of oral or systemic disease malformation or injury and the potential need for referral for diagnosis and treatment.	Prioritized	58 PREVENTIVE DENTAL SERVICES	Updated Guideline
D0220- D0330	<i>Change to descriptions, replacing "film" or "bitewings" with radiographic image. 14 codes</i>	Diagnostic		
D0340	CEPHALOMETRIC RADIOGRAPHIC IMAGES	Prioritized	647 DENTAL CONDITIONS (EG. MALOCCLUSION)	
D0364	Cone beam CT capture and interpretation with limited field of view less than one whole jaw	Excluded		
D0365	Cone beam CT capture and interpretation with field of view of one full dental arch - mandible	Excluded		
D0366	Cone beam CT capture and interpretation with field of view one full dental arch – maxilla with or without cranium	Excluded		
D0367	Cone beam CT capture and interpretation with field of view of both jaws with or without cranium	Excluded		
D0368	Cone beam CT capture and interpretation for TMJ series including two or more exposures	Excluded		
D0369	Maxillofacial MRI capture and interpretation	Excluded		
D0370	Maxillofacial ultrasound, capture and interpretation	Excluded		
D0371	Sialoendoscopy –capture and interpretation	Excluded		
D0380	Cone beam CT image capture with limited field of view – less than one whole jaw	Excluded		
D0381	Cone beam CT image capture with field of view of one full dental arch – mandible	Excluded		
D0382	Cone beam CT image capture with field of view one full dental arch – maxilla, with and without cranium	Excluded		

2012 CPT Code Review

Code	Code Description	List/File	Proposed April 2013 Placement	Notes
D0383	Cone beam CT image capture with field of view of both jaws, with or without cranium.	Excluded		
D0384	Cone beam CT capture images for TMJ series including two or more exposures	Excluded		
D0385	Maxillofacial MRI image capture	Excluded		
D0386	Maxillofacial ultrasound image capture	Excluded		
D0391	Interpretation of diagnostic image by a practitioner not associated with capture of the image, including report	Excluded		
D1206	Topical application of fluoride varnish	Prioritized	58 PREVENTIVE DENTAL SERVICES	
D1208	Topical application of fluoride	Prioritized	58 PREVENTIVE DENTAL SERVICES	
D2710	Crown resin-based composite (indirect)	Prioritized	494 ADVANCED RESTORATIVE DENTAL SERVICES (I.E. BASIC CROWNS)	
D2799	Provisional Crown – Further treatment or completion of a diagnosis necessary prior to final impression. Not to be used as a temporary crown for a routine prosthetic restoration.	Prioritized	676 DENTAL CONDITIONS WHERE TREATMENT RESULTS IN MARGINAL IMPROVEMENT	
D2929	Prefabricated porcelain/ceramic crown- primary tooth	Prioritized	621 ELECTIVE ADVANCED RESTORATIVE (INLAYS,ONLAYS,GOLD FOIL AND HIGH NOBLE METAL RESTORATIONS)	
D2940	Protective restoration Direct placement of a restorative material to protect tooth and/or tissue form. This procedure may be used to relieve pain, promote healing, or prevent further deterioration. Not to be used for endodontic access closure, or as a base or liner under restoration.	Prioritized	283 URGENT DENTAL SERVICES	
D2955	Post removal	Prioritized	676 DENTAL CONDITIONS WHERE TREATMENT RESULTS IN MARGINAL IMPROVEMENT	
D2980	Crown repair, necessitated by restorative material failure	Prioritized	372 BASIC RESTORATIVE DENTAL SERVICES	
D2981	Inlay repair, necessitated by restorative material failure.	Prioritized	621 ELECTIVE ADVANCED RESTORATIVE (INLAYS,ONLAYS,GOLD FOIL AND HIGH NOBLE METAL RESTORATIONS)	
D2982	Onlay repair, necessitated by restorative material failure	Prioritized	621 ELECTIVE ADVANCED RESTORATIVE (INLAYS,ONLAYS,GOLD FOIL AND HIGH NOBLE METAL RESTORATIONS)	
D2983	Veneer repair, necessitated by restorative material failure	Prioritized	675 DENTAL CONDITIONS WHERE TREATMENT IS CHOSEN PRIMARILY FOR AESTHETIC CONSIDERATIONS	
D2990	Resin infiltration of incipient smooth surface lesions – placement of an infiltrating resin restoration for strengthening, stabilizing and/or limiting the progression of the lesion	Prioritized	676 DENTAL CONDITIONS WHERE TREATMENT RESULTS IN MARGINAL IMPROVEMENT	

Code	Code Description	List/File	Proposed April 2013 Placement	Notes
D3352	Apexifaction/recalcification/pulpal regeneration) - interim medication replacement. For visits in which the intra-canal medication is replaced with new medication. Includes any necessary radiographs."	Prioritized	283 URGENT DENTAL SERVICES	
D4210	Gingivectomy or gingivoplasty - four or more contiguous teeth or bounded teeth spaces per quadrant. It is performed to eliminate suprabony pockets or to restore normal architecture when gingival enlargements or asymmetrical or unaesthetic topography is e	Prioritized	232 BASIC PERIODONTICS	Updated Guideline
D4211	Gingivectomy or gingivoplasty -four or more contiguous teeth tooth bounded spaces per quadrant. It is performed to eliminate suprabony pockets or to restore normal architecture when gingival enlargements or asymmetrical or unaesthetic topography is evide	Prioritized	232 BASIC PERIODONTICS	Updated Guideline
D4212	Gingivectomy or gingivoplasty - to allow access for restorative procedures - per tooth	Prioritized	232 BASIC PERIODONTICS	Updated Guideline
D4260	Osseous surgery - (including flap entry & closure - four or more contiguous teeth or tooth bonded spaces per quadrant. The procedure modifies the bony support of teeth by reshaping the alveolar process to achieve a more physiologic form. This must inclu	Prioritized	522 ADVANCED PERIODONTICS	
D4261	Osseous surgery - one to three contiguous teeth or tooth bonded spaces per quadrant. The procedure modifies the bony support of teeth by reshaping the alveolar process to achieve a more physiologic form. This must include the removal of supporting bone	Prioritized	523 ADVANCED PERIODONTICS	
D4266	Guided tissue regeneration -- resorbable barrier, per site This procedure does not include flap entry or closure, or, when indicated, wound debridement, osseous contouring, bone replacement grafts, and placement of biologic materials to aid in osseous reg	DMAP Excluded File	DMAP Excluded File	

Code	Code Description	List/File	Proposed April 2013 Placement	Notes
D4267	Guided tissue regeneration -- non-resorbable barrier, per site (includes membrane removal) This procedure does not include flap entry or closure, or, when indicated, wound debridement, osseous contouring, bone replacement grafts, and placement of biologic	DMAP Excluded File		
D4277	Free soft tissue graft procedure (including donor site surgery) - first tooth or edentulous tooth site in graft	Prioritized	522 ADVANCED PERIODONTICS (E.G. SURGICAL PROCEDURES AND SPLINTING)	
D4278	Free soft tissue graft procedure (including donor site surgery) -each additional contiguous tooth position in same graft site	Prioritized	522 ADVANCED PERIODONTICS (E.G. SURGICAL PROCEDURES AND SPLINTING)	
D4381	Localized delivery of antimicrobial agents via controlled release vehicle into diseased crevicular tissue, per tooth. FDA approved subgingival delivery devices containing antimicrobial medication(s) are inserted into periodontal pockets to suppress the p	Prioritized	522 ADVANCED PERIODONTICS	
D6051	Interim abutment - includes placement and removal. A healing cap is not an interim abutment	Prioritized	648 IMPLANTS (I.E. IMPLANT PLACEMENT AND ASSOCIATED CROWN OR PROSTHESIS)	
D6056	Prefabricated abutment - includes modification and placement. Modification of a prefabricated abutment may be necessary	Prioritized	648 IMPLANTS	
D6057	Custom fabricated abutment - includes placement – Created by a laboratory process specific for an individual application	Prioritized	648 IMPLANTS	
D6101	Debridement of a periimplant defect and surface cleaning of exposed implant surfaces, including flap entry and closure	Prioritized	648 IMPLANTS	
D6102	Debridement and osseous contouring of a periimplant defect; includes surface cleaning of exposed implant surfaces and flap entry and closure	Prioritized	648 IMPLANTS	
D6103	Bone graft for repair of periimplant defect – not including flap entry and closure or when indicated, placement of a barrier membrane or biologic materials to aid in osseous regeneration	Prioritized	648 IMPLANTS	

Code	Code Description	List/File	Proposed April 2013 Placement	Notes
D6104	Bone graft at time of implant placement – placement of a barrier membrane, or biologic materials at aid in osseous regeneration are reported separately	Prioritized	648 IMPLANTS	
D6253	Provisional Pontic – Further treatment or completion of a diagnosis necessary prior to final impression. Not be used as a temporary pontic for routine prosthetic fixed partial dentures.	Prioritized	621 ELECTIVE ADVANCED RESTORATIVE (INLAYS, ONLAYS, GOLD FOIL AND HIGH NOBLE METAL RESTORATIONS)	
D6793	Provisional Retainer Crown – Further treatment of completion or a diagnosis necessary prior to final impression. Not be used as a temporary retainer crown for routine prosthetic fixed partial dentures.	Prioritized	621 ELECTIVE ADVANCED RESTORATIVE (INLAYS, ONLAYS, GOLD FOIL AND HIGH NOBLE METAL RESTORATIONS)	
D6975	Coping	Prioritized	631 COMPLEX PROSTHODONTICS	
D6980	Fixed partial denture repair, repair necessitated by restorative material failure	Prioritized	372 BASIC RESTORATIVE DENTAL WORK	
D7921	Collection and application of autologous blood concentrate product	Excluded		
D7951	Sinus augmentation with bone or bone substitutes via a lateral open approach - The augmentation of the sinus cavity to increase alveolar height for reconstruction of edentulous portions of the maxilla. This procedure is performed via a lateral open approach. This includes obtaining the bone or bone substitutes. Placement of a barrier membrane if used should be reported separately.	Prioritized	648 DENTAL CONDITIONS (EG. MISSING TEETH)	
D7952	Sinus augmentation via a vertical approach - The augmentation of the sinus to increase alveolar height by vertical access through the ridge crest by raising the floor of the sinus and grafting as necessary. This includes obtaining the bone or bone substitutes.	Prioritized	648 DENTAL CONDITIONS (EG. MISSING TEETH)	
D9972	External bleaching per arch - performed in office	Prioritized	675 COSMETIC DENTAL SERVICES	
D9975	External bleaching - external bleaching system for applications - per arch includes materials and fabrication of custom trays	Prioritized	675 COSMETIC DENTAL SERVICES	

Evaluation & Management (E&M) Lines

1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,61,62,63,64,65,66,67,68,69,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,87,88,89,90,91,93,94,95,96,97,98,99,100,101,102,104,106,107,108,109,111,112,113,114,115,116,117,118,119,120,121,122,123,124,126,127,128,129,130,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,171,173,174,175,176,178,179,180,181,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,199,200,201,202,203,204,205,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,233,234,235,236,237,238,239,240,241,242,243,244,245,246,248,249,250,251,252,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,315,316,317,318,319,320,321,323,324,325,326,327,328,329,330,331,332,334,335,336,337,338,339,340,341,342,343,344,345,347,348,349,351,352,353,354,355,356,357,360,361,362,363,364,365,366,367,368,369,370,371,375,376,377,378,379,380,381,382,383,384,385,386,387,388,389,390,391,394,395,396,397,398,400,402,403,404,405,406,407,408,409,410,412,413,415,416,417,418,419,420,421,422,423,424,425,426,427,428,429,430,431,432,433,434,435,437,438,439,440,441,442,443,444,445,446,447,448,449,450,451,452,453,454,455,457,458,459,460,461,462,463,465,466,467,469,470,471,472,473,474,475,476,478,479,481,482,483,484,485,486,487,488,489,490,492,493,495,496,497,498,499,500,501,502,503,504,505,506,507,508,509,510,511,512,514,515,516,517,518,519,521,523,526,527,528,529,530,532,534,535,536,537,538,539,541,542,543,544,545,546,547,549,550,551,552,553,554,555,556,559,560,561,562,563,564,565,566,567,568,569,570,571,572,573,574,575,576,577,578,579,580,581,582,583,585,589,591,592,594,595,596,597,598,599,600,601,602,603,604,605,606,607,608,609,610,611,613,614,615,616,617,618,619,620,622,623,624,625,627,628,630,634,635,636,637,638,639,641,642,643,644,645,646,649,650,651,652,653,655,656,658,659,660,661,662,663,664,665,666,667,668,669,670,671,673,674,675,676,678,680,681,682,683,684,685,686,687,688,689,690,691,692

Appendix B

New Guidelines

New Guidelines for the April 1, 2013 Prioritized List

GUIDELINE NOTE XXX, CHEMODENERVATION OF THE BLADDER

Line 351

Chemodenervation of the bladder (CPT 55287) is included on this line only for treatment of overactive bladder caused by spinal cord injury, multiple sclerosis, and other spinal cord diseases in patients in whom appropriate pharmacologic therapy have proven to be ineffective or poorly tolerated.

New Guidelines for the October 1, 2014 ICD-10 Prioritized List

GUIDELINE XXX, GENDER DYSPHORIA

Line 521

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

Appendix C

Revised Guidelines

DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE

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

A) 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.2.2011~~42~~ (4/22/10 4/27/12). 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 **GUIDELINE NOTE 3, PROPHYLACTIC TREATMENT FOR PREVENTION OF BREAST CANCER IN HIGH RISK WOMEN** 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 Cancer Screening. V.1.2012 (5/2/12).

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.

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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 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 (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): Cover for diagnostic evaluation of individuals with intellectual disability/developmental delay; multiple congenital anomalies; or, Autism Spectrum Disorder accompanied by at least one of the following: dysmorphic features including macro or microcephaly, congenital anomalies, or intellectual disability/developmental delay in addition to those required to diagnose Autism Spectrum Disorder.

2) CPT 81229, Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and 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 consanguinity AND recessive disease is suspected, OR UPD (uniparental disomy) is suspected, OR other suspected mechanism that is not detected by the oligo microarrays (CPT 81228).

3) Array-based evaluation of multiple molecular probes (CPT 88384-88386) will be covered for diagnostic evaluation of individuals with intellectual disability/developmental delay; multiple congenital anomalies; or, Autism Spectrum Disorder for 2012.

4) 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.

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5) 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. 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. 81330, SMPD1 (sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)
- f. 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. CPT 81223, CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; full gene sequence: covered for patients who are symptomatic or who have positive newborn screening for CF AND genetic testing for common mutations is negative AND if the patients ethnicity has <90% coverage by common mutation panels.
- c. CPT 81224, CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; intron 8 poly-T analysis (eg, male infertility): Covered only after genetic counseling.
- d. CPT 81240, F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant: Not covered for routine testing in the following circumstances: (1) adults with idiopathic venous thromboembolism. (2) Asymptomatic adult family members of

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patients with idiopathic venous thromboembolism and F5 mutation, for the purpose of considering primary prophylactic anticoagulation. Test may have clinical utility in other circumstances, e.g. family history of coagulopathy, deciding short range anticoagulation therapy, problems with anticoagulation therapy management, multiple pregnancy losses.

- e. CPT 81241, F5 (coagulation Factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant: Not covered for routine testing in the following circumstances: (1) adults with idiopathic venous thromboembolism. (2) Asymptomatic adult family members of patients with idiopathic venous thromboembolism and F5 mutation, for the purpose of considering primary prophylactic anticoagulation. Test may have clinical utility in other circumstances, e.g. family history of coagulopathy, deciding short range anticoagulation therapy, problems with anticoagulation therapy management, multiple pregnancy losses.
 - 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. 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.

GUIDELINE NOTE 17, PREVENTIVE DENTAL CARE

Line 58

Dental cleaning and fluoride treatments are 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.](#)

Appendix C

GUIDELINE NOTE 53, BASIC PERIODONTICS

Line 232

Only for the treatment of severe drug-induced hyperplasia (D4210, D4211, [D4212](#)). Payable only when there are pockets of 5 mm or greater (D4341).

~~GUIDELINE NOTE 91, ONE SURFACE POSTERIOR COMPOSITE RESTORATIONS~~

Line 372

~~HCPSC code D2391 is only included on this line for one surface posterior composite restorations on occlusal surfaces and class V surfaces in the esthetic zone (buccal surfaces of teeth 3,4,5,12,13,14,19,20,21,28,29,30,A,B,I,J,K,L,S,T).~~

GUIDELINE NOTE 51, CHRONIC OTITIS MEDIA WITH EFFUSION

Line 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](#)).

[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](#) ~~c~~Children with chronic OME present for 3 months or longer. ~~or~~ [Children](#) with language delay, learning problems, or significant hearing loss ~~at any time~~ should have hearing testing [upon diagnosis](#). Children with chronic OME who are not at risk [for language 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.

For the child who has had chronic OME and who has a hearing deficiency in the better-hearing ear of 25 dB or greater, myringotomy with tube insertion [is](#) recommended after a total of 4 to 6 months of effusion with a documented hearing deficit.

Adenoidectomy [is not indicated at the time of first pressure equalization tube insertion](#). ~~It may be indicated in~~ ~~is an appropriate surgical treatment for chronic OME~~ in children over 3 years ~~with~~ [who are having](#) their second set of tubes. ~~First time tubes are not an indication for an adenoidectomy.~~

[Tube insertion should be covered for patients with craniofacial anomalies, Down's syndrome, cleft palate, and patients with speech and language delay along with co-morbid hearing loss.](#)

Section 3

Straightforward Items

Coronary Brachytherapy

Issue:

During the 2013 CPT code review of cardiac stenting, HERC staff identified that the CPT code for coronary brachytherapy is on multiple inappropriate lines.

Description: Intracoronary brachytherapy with gamma or beta radioactive ribbons for the management of in-stent restenosis of native coronary vessels following successful PTCA. Multiple contraindications exist, including acute MI, left ventricular ejection fraction <40%, and type of lesion.

Current list placement: CPT code 92974 (Transcatheter placement of radiation delivery device for subsequent coronary intravascular brachytherapy) is currently on multiple lines (approximately 40). It is only used for coronary artery stent issues. At the 2013 CPT code review, cardiac stenting was limited to 4 lines with coronary artery disease diagnoses. The coronary brachytherapy code is therefore on multiple lines that are inappropriate.

Recommendation:

- 1) Remove 92974 from all current lines except
 - i. **51** CORONARY ARTERY ANOMALY
 - ii. **76** ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION
 - iii. **108** HEART FAILURE
 - iv. **195** CHRONIC ISCHEMIC HEART DISEASE

Section 4

New Discussion Items

External Elements Exposure Issue Summary

Question: Should changes in coverage be made for a variety of “exposure” to element conditions?

Question Source: Jim Beggs, Medical Director, CCC

Issue:

Dr. Beggs raised concerns that motion sickness is covered for OHP, and simultaneously realized that the 994 series probably needed a re-look. He raised concerns as to whether OHP should cover G-force and weightlessness complications or exhaustion. He also raised the concern that many of these codes appear to be “secondary descriptors rather than primary illnesses and coverage should perhaps derive from their specific effect rather than how it happens.”

994 Effects of other external causes

Excludes: certain adverse effects not elsewhere classified (995.0-995.8)

994.0 Effects of lightning ➡ COVERED

Shock from lightning
Struck by lightning NOS

Excludes:
burns (940.0-949.5)

994.1 Drowning and nonfatal submersion ➡ COVERED

Bathing cramp
Immersion

994.2 Effects of hunger ➡ NOT Covered

Deprivation of food

Starvation

994.3 Effects of thirst ➡ NOT Covered

Deprivation of water

994.4 **Exhaustion** due to exposure ➡ COVERED

994.5 **Exhaustion** due to excessive exertion ➡ COVERED

Exhaustion due to overexertion

994.6 **Motion sickness** ➡ COVERED

Air sickness

Seasickness

Travel sickness

994.7 Asphyxiation and strangulation ➡ COVERED

Suffocation (by):

bedclothes
cave-in
constriction
mechanical
plastic bag
pressure

External Elements Exposure Issue Summary

strangulation

Excludes:

asphyxia from:

carbon monoxide (986)

inhalation of food or foreign body (932-934.9)

other gases, fumes, and vapors (987.0-987.9)

994.8 Electrocution and nonfatal effects of electric current ➡ COVERED

Shock from electric current

Shock from electroshock gun (taser)

Excludes:

electric burns (940.0-949.5)

994.9 Other effects of external causes ➡ COVERED

Effects of:

abnormal gravitational [**G**] forces or states

weightlessness

HERC Staff additional background:

994.2 and 994.3 are in the funded region of the List, on Line 132.

Code	Description	Line Placement
994.2	Effects of hunger	132 PHYSICAL AND SEXUAL ABUSE INCLUDING RAPE
994.3	Effects of thirst	132 PHYSICAL AND SEXUAL ABUSE INCLUDING RAPE

HERC Staff Recommendations

If recommendation column is blank, no change is recommended.

Line 187 CONDITIONS INVOLVING EXPOSURE TO NATURAL ELEMENTS (EG. LIGHTNING STRIKE, HEATSTROKE)		
Code	Description	Recommendation
692.77	Sunburn of third degree	
991.0	Frostbite of face	
991.1	Frostbite of hand	
991.2	Frostbite of foot	

External Elements Exposure Issue Summary

Line 187 CONDITIONS INVOLVING EXPOSURE TO NATURAL ELEMENTS (EG. LIGHTNING STRIKE, HEATSTROKE)		
Code	Description	Recommendation
991.3	Frostbite of other and unspecified sites	
991.4	Immersion foot	
991.5	Chilblains	
991.8	Other specified effects of reduced temperature	
991.9	Unspecified effect of reduced temperature	
992.0	Heat stroke and sunstroke	
992.1	Heat syncope	
992.2	Heat cramps	
992.3	Heat exhaustion, anhydrotic	
992.4	Heat exhaustion due to salt depletion	
992.5	Heat exhaustion, unspecified	
992.6	Heat fatigue, transient	
992.7	Heat edema	
992.8	Other specified heat effects	
992.9	Unspecified effects of heat and light	688 DERMATOLOGICAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
993.2	Other and unspecified effects of high altitude	
994.0	Effects of lightning	
994.1	Drowning and nonfatal submersion	
994.4	Exhaustion due to exposure	
994.5	Exhaustion due to excessive exertion	691 MUSCULOSKELETAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
994.6	Motion sickness	539 VERTIGINOUS SYNDROMES AND OTHER DISORDERS OF VESTIBULAR SYSTEM
994.7	Asphyxiation and strangulation	
994.8	Electrocution and nonfatal	

External Elements Exposure Issue Summary

Line 187 CONDITIONS INVOLVING EXPOSURE TO NATURAL ELEMENTS (EG. LIGHTNING STRIKE, HEATSTROKE)		
Code	Description	Recommendation
	effects of electric current	
994.9	Other effects of external causes (abnormal gravitational forces or states weightlessness)	
995.89	Other specified adverse effects, not elsewhere classified (hypothermia due to anesthesia)	

And with ICD-10

Code	Description	Prior Placement	Recommended Placement
992.9	Unspecified effects of heat and light	187	688
994.5	Exhaustion due to excessive exertion	187	691
994.6	Motion sickness	187	539
T67.9xxA	Effect of heat and light, unspecified, initial encounter	187	187
T67.9xxD	Effect of heat and light, unspecified, subsequent encounter	DMAP Ancillary Codes File	688
T73.3xxA	Exhaustion due to excessive exertion, initial encounter	DMAP Ancillary Codes File,187	691
T75.3xxA	Motion sickness, initial encounter	DMAP Ancillary Codes File,187	539

Stereotactic Radiosurgery for Intracranial Arteriovenous Malformations

Question: Should stereotactic radiosurgery be covered for treatment of intracranial arteriovenous malformations (AVMs)?

Question source: OHP Medical Director

Issue: cerebral AVMs (ICD-9 747.81) are on Line 201 SUBARACHNOID AND INTRACEREBRAL HEMORRHAGE/HEMATOMA; CEREBRAL ANEURYSM; COMPRESSION OF BRAIN. There are various treatments on this line, including embolization and intracranial surgery. Intracranial stereotactic radiosurgery (CPT 77263-77295, 77300, 77332-77336, 77370-77372, 77402-77416, 77432) is on various lines for treatment of benign and malignant tumors of the CNS. However, it is currently not covered for treatment of AVMs.

From Dr. Chris Kirk:

We have a member with “anomaly of cerebrovascular system” – ICD-9 code 747.81. It is a deep parietal AVM. He cannot have surgery due to its deep location. It is not amenable to embolization because of its lack of a specific arterial vessel that can be embolized. The team at OHSU would like to treat him with Stereotactic Radiosurgery (CPT codes: 77263, 77280, 77295, 77300, 77334, 77336, 77370, 77414, 77417, 77432, 77371, 77372) They make the claim that this is “...a commonly accepted treatment method for this patient’s situation...” and that it is supported in the literature (they offered no citations).

Evidence

- 1) **Friedlander 2007**, review of AVMs
 - a. Radiosurgery is often recommended if an arteriovenous malformation is less than 3 cm in diameter and is located in an eloquent area where surgery is likely to cause a neurologic deficit.
 - b. Although data from randomized trials to guide the choice of intervention are lacking, treatment (surgical resection, radiosurgery, embolization, or a combination of these) is generally considered appropriate for arteriovenous malformations that are grade I to III.^{24,33} The choice of therapy will depend on the specific features of the lesion, with consideration of the age of the patient, presence or absence of bleeding and associated aneurysms, diameter and location of associated aneurysms, and pattern of venous drainage.
- 2) **Fleetwood 2002**, review of AVMs
 - a. All three treatment modalities—microsurgery, endovascular embolisation, and radiosurgery—have an established role in treatment of patients with arteriovenous malformations

Stereotactic Radiosurgery for Intracranial Arteriovenous Malformations

3) Other policies

a. Aetna 2012

- i. Cranial stereotactic radiosurgery with a gamma knife, Cyberknife, or linear accelerator (LINAC) is considered medically necessary when used for treatment of members with symptomatic, small (less than 3 cm) arterio-venous (AV) malformations, aneurysms, and benign tumors (acoustic neuromas (vestibular schwannomas), meningiomas, hemangiomas, pituitary adenomas, craniopharyngiomas, and neoplasms of the pineal gland) if the lesion is unresectable due to its deep intracranial location or if the member is unable to tolerate conventional operative intervention

b. Cigna 2012

- i. Covers stereotactic radiosurgery for arteriovenous malformation of the brain or spine

Summary: intracranial stereotactic radiosurgery appears to be a standard, accepted treatment for certain patients with AVMs

Recommendation:

- 1) Add intracranial stereotactic radiosurgery to line 201 SUBARACHNOID AND INTRACEREBRAL HEMORRHAGE/HEMATOMA; CEREBRAL ANEURYSM; COMPRESSION OF BRAIN
 - a. 77263-77295, 77300, 77332-77336, 77370-77372, 77402-77416, 77432

CLINICAL PRACTICE

Arteriovenous Malformations of the Brain

Robert M. Friedlander, M.D.

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A 51-year-old woman presents with a generalized tonic–clonic seizure. After a brief postictal period, she recovers fully and does not report headache or other neurologic symptoms. She takes no medications and her medical history is unremarkable. Computed tomography of the head suggests a right occipital arteriovenous malformation, without evidence of hemorrhage. Computed tomographic angiography, magnetic resonance imaging, and magnetic resonance angiography of the brain show a right occipital arteriovenous malformation, 3.5 cm in diameter, as well as a feeding-artery aneurysm, 1.5 cm in diameter. How should her case be further evaluated and managed?

THE CLINICAL PROBLEM

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Arteriovenous malformations of the brain are focal abnormal conglomerations of dilated arteries and veins within brain parenchyma, in which a loss of normal vascular organization at the subarteriolar level and a lack of a capillary bed result in abnormal arteriovenous shunting (Fig. 1). Arteriovenous malformations can occur anywhere in the central nervous system; in this article, I focus on those in the brain. Small arteries involved in arteriovenous malformation are deficient in the smooth-muscle layer.¹ The tangle of abnormal arteries and veins in the malformation (often referred to as the arteriovenous malformation nidus) are connected by one fistula or, more commonly, several fistulas. The direct arteriovenous connection results in high-pressure vascular channels, particularly in veins with fibromuscular thickening and incompetent elastic lamina; these veins are at risk of rupture, often with catastrophic results.

The most common presenting sign of an arteriovenous malformation is intracerebral hemorrhage (occurring in 42 to 72% of clinically apparent arteriovenous malformations).²⁻⁷ A first hemorrhage most commonly occurs in patients between 20 and 40 years of age.²⁻⁴ Data are conflicting regarding associations between age and the risk of hemorrhage, with studies reporting either a higher risk in older patients, in younger patients, or in both (bimodal peaks) or a constant risk over time.^{4,5,8,9} Sex does not appear to affect the risk of rupture.^{6,10,11} Hemorrhage of arteriovenous malformations accounts for approximately 2% of all strokes.^{10,12} Other presenting signs of arteriovenous malformations include seizures, mass effect (from direct compression or swelling related to the malformation, putting pressure on surrounding structures), and ischemic steal (due to preferential low-resistance blood flow through the arteriovenous malformation, resulting in the hypoperfusion of adjacent structures). Even in the absence of bleeding, headaches (specifically migraines) have been associated with arteriovenous malformations.¹³

The prevalence of arteriovenous malformation is estimated at approximately 0.01% of the general population, but reported rates range from 0.001% to 0.52%.^{3,10,11,14,15} The lesions are thought to be congenital in origin. Although occa-

Seminar

Arteriovenous malformations

Ian G Fleetwood, Gary K Steinberg

Arteriovenous malformations of the brain are congenital vascular lesions that affect 0.01–0.50% of the population, and are generally present in patients aged 20–40 years. The usual clinical presentations are haemorrhage, seizures, progressive neurological deficit, or headache. Results of natural history studies have shown a yearly haemorrhage rate of 1–4%. Frequency of rebleeding has increased over the years, and several factors that increase risk of haemorrhage have been identified. Although substantial, the morbidity associated with haemorrhages could be less than previously thought. Over the past decade, great advances have been made in application of endovascular embolisation techniques, stereotactic radiosurgery, and microsurgery, allowing effective multidisciplinary treatment of arteriovenous malformations, including those previously deemed to be untreatable. Increasing attention has been paid to management of flow-related aneurysms associated with these malformations. Finally, many reports of recurrent arteriovenous malformations have coincided with new theories regarding the embryogenesis of these disorders and laboratory work suggesting their proliferative potential.

During the “decade of the brain” (1990–2000) knowledge of cerebral arteriovenous malformations, among other neurosurgical disorders has greatly advanced. As enigmatic as these lesions remain, we have gained a better understanding of their pathogenesis, clinical presentation, and natural history. Major developments have also been made in microsurgical, endovascular, and radiosurgical treatments. In this seminar, rather than providing an exhaustive review of all aspects of arteriovenous malformations, we summarise the most recent and relevant published work, focusing on the past 5 years, and in particular on new information that changes our approach to patients with arteriovenous malformations. We will also discuss several studies that have focused on the outcome of these patients after treatment. For a more detailed assessment of the present state of treatment for arteriovenous malformations, we recommend recent reviews^{1–3} and the American Heart Association guidelines for management of arteriovenous malformations.⁴

Pathology

Few developments have been made in pathological findings of arteriovenous malformations, but, Martin and Vinters⁵ provide a good overview of expected findings. Arteriovenous malformations are lesions that are defined by presence of arteriovenous shunting through a nidus of coiled and tortuous vascular connections that connect feeding arteries to draining veins (figures 1–3). Histologically, cells found within the nest generally show chronic reactive changes and are thought to be non-functioning. Vascular structures retain the characteristic feeding arterial and draining venous components, but no capillaries are seen between these two elements, creating direct arteriovenous shunting. Arterial and venous elements both show hypertrophy in their walls.

Lancet 2002; **359**: 863–73

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Microscopically, the elastic lamina of the arterial intimal layer is mostly intact, but might show some degradation or deficiencies. The thickened veins can be discerned by their size and the absence of elastic staining. Both elements can also show hyperplasia of the smooth-muscle cells in the tunica media. If haemorrhage has occurred, the surrounding parenchyma will have evidence of gliosis and haemosiderin staining.

Embryogenesis

Arteriovenous malformations have long been thought to be either a persistent or reconstituted abnormal connection between the arterial and venous systems. In 1987, Yasargil⁶ postulated that, rather than being a simple structural connection, these lesions might be a “proliferative capillaropathy”. This suggestion that arteriovenous malformations are dynamic in nature has been lent support by several case reports (described below), and by two recent theories. Most theories about the embryogenesis of these lesions include a definitive statement about their congenital nature, and attribute them to either persistence of a primitive arteriovenous connection or development of such a connection after its initial closure. In 1996, Mullan and colleagues⁷ showed that arteriovenous malformations are generally impossible to identify in utero or with perinatal ultrasound, suggesting that they are either too small to detect in these

Search strategy and selection criteria

Data for this seminar were identified by searches of BioMedNet and PubMed with the search terms “arteriovenous malformation” or “AVM” in combination with the terms “cerebral” or “intracranial”. We then searched these publications using the terms “epidemiology”, “natural history”, “hemorrhage”, “aneurysm”, “treatment”, “surgery”, and “radiosurgery”. We focused on publications in the past 5 years, but did not exclude commonly referenced and highly regarded older publications. Relevant articles not identified with the search strategy described above, but referenced in the bibliographies of these papers, could also be included. Several recent review articles and book chapters were also included because they provide comprehensive overviews that, in some cases, were beyond the scope of this seminar. The reference list was subsequently modified during the peer-review process on the basis of comments from reviewers.

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 Search

Clinical Policy Bulletin: Stereotactic Radiosurgery

Number: 0083

Policy

Aetna considers stereotactic radiosurgery medically necessary according to the following selection criteria.

- I. Cranial stereotactic radiosurgery with a gamma knife, Cyberknife, or linear accelerator (LINAC) is considered medically necessary when used for *any* of the following indications:
 - A. For treatment of members with symptomatic, small (less than 3 cm) arterio-venous (AV) malformations, aneurysms, and benign tumors (acoustic neuromas (vestibular schwannomas), meningiomas, hemangiomas, pituitary adenomas, craniopharyngiomas, and neoplasms of the pineal gland) if the lesion is unresectable due to its deep intracranial location or if the member is unable to tolerate conventional operative intervention; *or*
 - B. For members with trigeminal neuralgia that has not responded to other more conservative treatments (see [CPB 0374 - Trigeminal Neuralgia Surgery](#)); *or*
 - C. For treatment of brain malignancies (primary tumors and/or metastatic lesions).
- II. Stereotactic body radiation therapy (SBRT) with a gamma knife, Cyberknife, or linear accelerator (LINAC) is considered medically necessary for localized malignant conditions within the body where highly precise application of high-dose radiotherapy is required (e.g., lung or liver metastases not amenable to surgery, medically inoperable early stage lung cancer, primary liver cancer not amenable to surgery, spinal and para-spinal tumors, not an all inclusive list).
- III. Fractionated stereotactic radiotherapy is considered medically necessary when criteria for stereotactic radiosurgery are met. Fractionated stereotactic radiotherapy is useful for treatment of tumors in hard-to-reach locations, tumors with very unusual shapes, or for tumors located in such close proximity to a vital structure (e.g., optic nerve or hypothalamus) that even a very accurate high-dose single fraction of stereotactic radiosurgery could not be tolerated.
- IV. Stereotactic proton beam radiosurgery: please see [CPB 0270 - Proton Beam and Neutron Beam Radiotherapy](#).

Aetna considers stereotactic radiosurgery experimental and investigational for all other indications because its effectiveness for these indications has not been established including:

- Cluster headaches
- Epilepsy (except when associated with treatment of AV malformations or brain tumors)
- Mammographic microcalcification
- Parkinson's disease.

Background

With any external beam radiation therapy, the highest dose of radiation develops where multiple beams intersect. Thus, the fewer beams there are, the greater the dose reaching other areas traversed by the

Policy History

> [Last Review](#): 04/24/2012
 Effective: 11/29/1995
 Next Review: 01/24/2013
 > [Review History](#)
 > [Definitions](#)

Additional Information

> [Clinical Policy Bulletin Notes](#)



Cigna Medical Coverage Policy

Subject Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiation Therapy (SBRT)

Effective Date 6/15/2012
Next Review Date 4/15/2013
Coverage Policy Number 0110

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Hyperlink to Related Coverage Policies

- [Inpatient Admission for Radiation Therapy](#)
- [Intensity-Modulated Radiation Therapy \(IMRT\)](#)
- [Neutron Beam Therapy](#)
- [Proton Beam Therapy for Intracranial and Skull Base Tumors](#)
- [Proton Beam Therapy for Lung Cancer](#)
- [Proton Beam Therapy for Ocular Melanoma, Ocular Hemangiomas and Macular Degeneration](#)
- [Proton Beam Therapy for Prostate Cancer](#)

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Coverage Policy

In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Cigna covers stereotactic radiosurgery including fractionated stereotactic radiotherapy and/or stereotactic body radiation therapy (e.g., Gamma Knife[®], CyberKnife[®], X-Knife[®], Peacock[®], Trilogy[™], TomoTherapy[®], Hi-Art[®], ONCOR[™], RapidArc[®]) as medically necessary for ANY of the following indications:

ONCOLOGY

- primary brain tumor other than glioma (e.g., meningioma, pituitary tumor, hemangioblastoma, acoustic neuroma [i.e. vestibular schwannoma], hypothalamic hamartoma)
- brain metastasis in an individual with limited tumor volume on presentation, good performance status (*ECOG or KPS), and controlled systemic disease
- recurrent brain metastasis in an individual who has not received whole brain radiotherapy and has controlled systemic disease
- symptomatic primary spinal tumor (e.g., neurological impairment, pain)

- symptomatic metastatic spinal tumor (e.g., neurological impairment, pain) for EITHER of the following:
 - tumor must be in a previously irradiated area
 - tumor type is known to be radio-resistant histology [e.g., renal cell carcinoma]
- uveal melanoma (melanoma of the uveal tract [iris, ciliary body, and choroid])
- nasopharyngeal cancer
- early stage (T1 or T2) non small-cell lung cancer (NSCLC) in an individual who is not a surgical candidate or refuses surgery
- symptomatic pulmonary metastasis in an individual with good performance status and controlled systemic disease
- unresectable primary renal cell carcinoma (RCC)
- metastatic RCC to the spine in an individual with good performance status
- metastatic RCC to the brain in an individual with limited tumor volume on presentation, good performance status, and controlled systemic disease
- unresectable hepatocellular carcinoma (HCC)
- metastatic colorectal cancer to the liver in an individual with limited tumor volume on presentation, good performance status, and controlled systemic disease
- low to intermediate risk** prostate cancer
- extracranial malignancy which is either in or adjacent to a previously irradiated volume, or located near a critical structure, where the risk of toxicity precludes use of another local modality

OTHER

- arteriovenous malformation of the brain or spine
- Parkinsonian or essential tremor that is refractory to medical management
- trigeminal neuralgia refractory to medical management

NOT COVERED

Cigna does not cover stereotactic radiosurgery including fractionated stereotactic radiotherapy and/or stereotactic body radiation therapy for any other indication, including but not limited to the following, because it is considered experimental, investigational or unproven (this list may not be all-inclusive):

- behavioral health disorders (e.g., obsessive-compulsive disorder)
- breast cancer
- epilepsy
- glioma
- pancreatic cancer

* Eastern Cooperative Oncology Group Performance Status

Grade definitions:

0 - Fully active, able to carry on all pre-disease performance without restriction

1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work

2 - Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours

3 - Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

4 - Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

5 - Dead (Oken, et al., 1982)

* Karnofsky Performance Status

Score definitions:

100% – normal, no complaints, no signs of disease

90% – capable of normal activity, few symptoms or signs of disease

80% – normal activity with some difficulty, some symptoms or signs

70% – caring for self, not capable of normal activity or work

60% – requiring some help, can take care of most personal requirements

50% – requires help often, requires frequent medical care

Personal History of Cancer V Codes

Question: should additional personal history of cancer diagnosis codes be on funded lines?

Question source: DMAP and HERC staff

Issue: Most V10 series codes (personal history of cancer) are located on funded lines. For many cancers, there is an altered screening schedule (more frequent colonoscopy in colon cancer, for example) or screening modality (e.g. breast MRI instead of mammogram in breast cancer) if a patient has a history of that cancer. Other cancer survivors may need periodic PET scans, X-rays, blood work, specialist visits, or other types of surveillance and follow up.

Most V10 codes are located on funded lines. However, 2 are located on unfunded lines and several are located on the Excluded List. These should be considered for movement to funded lines. There are several “unspecified” codes that are Excluded and should remain so.

Recommendation:

- 1) Adopt the changes outlined in the following table

Personal History of Cancer V Codes

Code	Code Description	Current Location	Proposed Location	Notes/Comments
V10.09	Personal history of malignant neoplasm of other gastrointestinal tract	Excluded	165 CANCER OF COLON, RECTUM, SMALL INTESTINE AND ANUS 277 CANCER OF RETROPERITONEUM, PERITONEUM, OMENTUM AND MESENTERY 341 CANCER OF PANCREAS 459 CANCER OF GALLBLADDER AND OTHER BILIARY	Indicated for use in ICD-9: cancer of pancreas, small intestine, gallbladder, retroperitoneum, and similar
V10.29	Personal history of malignant neoplasm of other respiratory and intrathoracic organs	Excluded	207 CANCER OF SOFT TISSUE 276 CANCER OF ENDOCRINE SYSTEM, EXCLUDING THYROID; CARCINOID SYNDROME 278 CANCER OF LUNG, BRONCHUS, PLEURA, TRACHEA, MEDIASTINUM AND OTHER RESPIRATORY ORGANS	Indicated for use in ICD-9: cancer of pleura, thymus, heart, mediastinum
V10.44	Personal history of malignant neoplasm of other female genital organs	Excluded	311 CANCER OF VAGINA, VULVA AND OTHER FEMALE GENITAL ORGANS	Indicated for use in ICD-9: cancer of vagina, vulva
V10.69	Personal history of other leukemia	Excluded	181 ACUTE NON-LYMPHOCYTIC LEUKEMIAS 310 CHRONIC LEUKEMIAS; POLYCYTHEMIA RUBRA VERA	Indicated for use in ICD-9: other specified leukemia (207 family), unspecified leukemia (208 family)
V10.79	Personal history of other lymphatic and hematopoietic neoplasms	Excluded	221 NON-HODGKIN'S LYMPHOMAS 249 ACUTE LYMPHOCYTIC LEUKEMIAS (ADULT) AND MULTIPLE MYELOMA 310 CHRONIC LEUKEMIAS; POLYCYTHEMIA RUBRA VERA	Indicated for use in ICD-9: other malignant neoplasms of lymphoid and histiocytic tissue (202 family), multiple myeloma and immunoproliferative neoplasms (203 family)
V10.88	Personal history of malignant neoplasm of other endocrine glands and related structures	622 SECONDARY AND ILL-DEFINED MALIGNANT NEOPLASMS	207 CANCER OF SOFT TISSUE	Indicated for use in ICD-9: cancer of connective tissue and soft tissue (171 family)
V10.91	Personal history of malignant neuroendocrine tumor	622	209 CANCER OF SKIN, EXCLUDING MALIGNANT MELANOMA 276 CANCER OF ENDOCRINE SYSTEM, EXCLUDING THYROID; CARCINOID SYNDROME 622 SECONDARY AND ILL-DEFINED MALIGNANT NEOPLASMS	Indicated for use in ICD-9: carcinoid tumor NOS, neuroendocrine tumor NOS, Merkel cell carcinoma

Personal History of Cancer V Codes

Section 5

Previously Discussed Items

Auricular Electro-Acupuncture

Issue: The new HCPCS code for auricular acupuncture was discussed at the December VBBS meeting. At that time, HERC staff indicated that there was not enough information available to make a placement determination for this code. Staff has consulted experts and reviewed additional materials.

Definition: Auricular electrostimulation involves the stimulation of acupuncture points on the ear. Devices, including the P-Stim and E-pulse, have been developed to provide ambulatory electrical stimulation over a period of several days. Auricular electrostimulation is being evaluated for a variety of conditions, including pain, depression, and anxiety. The P-Stim device is a single-use miniature electrical stimulator for auricular acupuncture points that is worn behind the ear with a self-adhesive electrode patch. A selection stylus that measures electrical resistance is used to identify 3 auricular acupuncture points.

Current List status:

New code: S8930 Electrical stimulation of auricular acupuncture points; each 15 minutes of personal one-on-one contact with the patient

Current lines with acupuncture CPT codes for traditional acupuncture:

- 1 PREGNANCY
- 5 ABUSE OR DEPENDENCE OF PSYCHOACTIVE SUBSTANCE
- 6 TOBACCO DEPENDENCE
- 15 HIV DISEASE (INCLUDING ACQUIRED IMMUNODEFICIENCY SYNDROME) AND RELATED OPPORTUNISTIC INFECTIONS
- 68 SUBSTANCE-INDUCED DELUSIONAL AND MOOD DISORDERS; INTOXICATION
- 70 SUBSTANCE-INDUCED DELIRIUM
- 212 DEPRESSION AND OTHER MOOD DISORDERS, MILD OR MODERATE
- 400 DISORDERS OF SPINE WITH NEUROLOGIC IMPAIRMENT
- 435 MIGRAINE HEADACHES
- 562 ACUTE AND CHRONIC DISORDERS OF SPINE WITHOUT NEUROLOGIC IMPAIRMENT
- 563 TENSION HEADACHES

Expert input:

Peter Martin, LAc, Associate Medical Director with CHP Group

Mr. Martin reported that the HCPCS code is likely used for payment for the device used for this type of acupuncture.

Auricular Electro-Acupuncture

Roger Batchelor, DAOM L.Ac., NCNM

Devices for full-body and ear acupuncture are typically the same, and usually simple. These devices are essential for acupuncture. It is comfortable for patients and efficient for practitioners. Research on conventional devices is extensive, such as the work of Becker and most notably Dr. Han, Ji-Sheng. Han led government research on acupuncture in China for 30 years, and found that electro acupressure or acupuncture (specifically alternating between 2 and 100 Hz) boosted all 5 known neurotransmitters in the cerebrospinal fluid. He published a wealth of research articles in English, searchable on PubMed, and presented at top-level scientific conferences internationally. For this, he was awarded China's top science prize a few years ago. Most LAc's are unaware of Dr. Han's work, but it provides rich scientific basis for ElectroAcupuncture (EA). Many acupuncturists use a simple 10 Hz if an alternating current is not available on their machines --many of my MD acupuncture colleagues use this as a convention. It was the waveform successfully applied on two acupoints on a patient's head during a 3 hour surgery at OHSU in 2004 that precluded the use of any chemical anesthesia. One EA device, called 'micro current,' markets something that claims great effects --although the patient does not feel anything. Some of my colleagues swear by these devices, attending special workshops by the manufacturer. As is the case with most medical devices, however, there is no independent research on them.

In the past, this was billed as Electro acupuncture, for slightly more than conventional. These devices do not require additional training nor capital investment, since the devices cost less than \$500, and great ones run for about \$300 or less. I've never understood why a separate code or cost was justified with these devices. This billing practice probably encouraged the use of EA by practitioners, which is harmless, but is not a good model for influencing practice for the sake of a few dollars.

The list makes sense. It is an essential practice for acute situations where hours of stimulation are needed, such as surgical or dental anesthesia/analgesia, or obstetric labor and delivery. It is interesting that every research article I surveyed that compared EA to conventional acupuncture for treating depression had superior results for EA: that was about a dozen articles in 2005. It makes a strong case for EA with this condition. EA is well known for pain of all types. I would not limit it to the pain conditions below. It would not be my first choice for pregnancy, but is essential for labor and delivery. Working at Hooper Detox, we found EA to help difficult detoxification, such as opiates.

Auricular Electro-Acupuncture

Other policies:

1) Wellmark BCBS 2012

- a. Electrical stimulation of auricular acupuncture points is considered **investigational**

2) Regence BCBS 2012

- a. Electrical stimulation of auricular acupuncture points is considered **investigational** for all indications, including but not limited to chronic and acute pain.

Recommendation:

- 1) Possible placements for S8930 (Electrical stimulation of auricular acupuncture points; each 15 minutes of personal one-on-one contact with the patient) are:
 - a. The excluded list
 - i. Investigational, acupuncturists may use traditional acupuncture CPT codes
 - b. Current acupuncture lines, as experts feel that this is useful and cost is not high
 - i. 1 PREGNANCY
 - ii. 5 ABUSE OR DEPENDENCE OF PSYCHOACTIVE SUBSTANCE
 - iii. 6 TOBACCO DEPENDENCE
 - iv. 15 HIV DISEASE (INCLUDING ACQUIRED IMMUNODEFICIENCY SYNDROME) AND RELATED OPPORTUNISTIC INFECTIONS
 - v. 68 SUBSTANCE-INDUCED DELUSIONAL AND MOOD DISORDERS; INTOXICATION
 - vi. 70 SUBSTANCE-INDUCED DELIRIUM
 - vii. 212 DEPRESSION AND OTHER MOOD DISORDERS, MILD OR MODERATE
 - viii. 400 DISORDERS OF SPINE WITH NEUROLOGIC IMPAIRMENT
 - ix. 435 MIGRAINE HEADACHES
 - x. 562 ACUTE AND CHRONIC DISORDERS OF SPINE WITHOUT NEUROLOGIC IMPAIRMENT
 - xi. 563 TENSION HEADACHES
 - c. Current acupuncture lines, with a guideline specifying that this code is not to be used for proprietary devices (see wording below)

GUIDELINE NOTE XXX AURICULAR ACUPUNCTURE

Lines 1, 5, 6, 15, 68, 70, 212, 400, 435, 562, 563

Auricular Electro-Acupuncture

HCPCS code S8930 is included on these lines for traditional electro-acupuncture. Use of proprietary electrical stimulation devices, such as P-Stim and E-pulse, is not included on these lines.

Contact Information

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and
Blue Shield
Medical Policy Analyst
P.O. Box 9232
Des Moines, IA
50306-9232

Auricular Electrostimulation

Medical Policy: 02.01.47

Original Effective Date: March 2012

Reviewed:

Revised:

Benefit Application

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This medical policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

This Medical Policy document describes the status of medical technology at the time the document was developed. Since that time, new technology may have emerged or new medical literature may have been published. This Medical Policy will be reviewed regularly and be updated as scientific and medical literature becomes available.

Description:

Auricular electrostimulation involves the stimulation of acupuncture points on the ear. Devices, including the P-Stim™ and E-pulse, have been developed to provide ambulatory electrical stimulation over a period of several days. Auricular electrostimulation is being evaluated for a variety of conditions, including pain, depression, and anxiety.

The P-Stim™ device is a single-use miniature electrical stimulator for auricular acupuncture points that is worn behind the ear with a self-adhesive electrode patch. A selection stylus that measures electrical resistance is used to identify 3 auricular acupuncture points. The P-Stim™ device connects to 3 inserted acupuncture needles with caps and wires. The device is pre-programmed to be on for 180 minutes, then off for 180 minutes. The maximum battery life for this single-use device is 96 hours.

The P-Stim™ (NeuroScience Therapy Corp) received marketing clearance through the U.S. Food and Drug Administration's (FDA) 510(k) process in 2006. The P-Stim™ is intended for use as an electro-acupuncture device to stimulate appropriate auricular acupuncture points. The E-pulse is a microprocessor-controlled battery-powered unit designed to administer auricular point nerve stimulation treatment for pain therapy over a 96-hour period.

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Medical Policy Manual

Topic: Auricular Electrostimulation

Date of Origin: March 2012

Section: Medicine

Approved Date: April 2, 2012

Policy No: 146

Effective Date: June 1, 2012

IMPORTANT REMINDER

Regence Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Auricular electrostimulation is a type of ambulatory electrical stimulation of acupuncture points on the ear. Devices, including the P-Stim™ and E-pulse, have been developed to provide continuous or intermittent stimulation over a period of several days. Also known as auricular electro-acupuncture, this type of electrostimulation is being evaluated for a variety of conditions, including pain, depression, and anxiety.

Regulatory Status

Both the P-Stim (NeuroScience Therapy Corp) and the E-pulse (AMM Marketing LLC) devices have received marketing clearance through the U.S. Food and Drug Administration's (FDA) 510(k) process for use in treating acute or chronic pain by a qualified practitioner of acupuncture.

Note: This policy does not address Cranial Electrostimulation Therapy, which is considered separately in DME Policy No. [83.06](#).

MEDICAL POLICY CRITERIA

Electrical stimulation of auricular acupuncture points is considered **investigational** for all indications, including but not limited to chronic and acute pain.

SCIENTIFIC EVIDENCE

The principal outcomes associated with treatment of pain due to any cause may include: relief of pain, improved functional level, and return to work. Relief of pain is a subjective outcome that is typically associated with a placebo effect. Therefore, data from adequately powered, blinded, randomized, sham-controlled trials (RCT) are required to control for the placebo effect, determine its magnitude, and determine whether any treatment effect from an auricular electrostimulation device provides a significant advantage over the placebo.

Treatment with an auricular electrostimulation device must also be evaluated in general groups of patients against the existing standard of care for the condition being treated. For example, in patients with pain symptoms, treatment with an auricular electrostimulation device should be compared to other forms of conservative therapy such as rest, non-steroidal anti-inflammatory medications, physical therapy, or steroid injections.

Literature Appraisal

Several randomized controlled trials (RCTs) have been reported on the use of the P-stim device and are the focus of this policy.

- In 2004, Sator-Katzenschlager et al. reported a randomized double-blind controlled study of auricular electro-acupuncture compared to conventional manual auricular acupuncture in 61 patients with chronic low back pain (duration of at least 6 months).^[1] All needles were connected to the P-Stim device; in the control group, devices were applied without electrical stimulation. Treatment was performed once weekly for 6 weeks, with needles withdrawn 48 hours after insertion. Patients received questionnaires assessing pain intensity and quality, psychological well-being, activity level, and quality of sleep using visual analog scale (VAS). There was a significant improvement in pain at up to 18 weeks' follow-up. Auricular electro-acupuncture resulted in greater improvement in the outcome measures than that of the control group. For example, at 18-week follow-up, VAS pain intensity was less than 5 in the control group and less than 2 in the electro-acupuncture. This study is limited by the small number of participants. In 2003, this group of investigators had reported similar effects in a small randomized study of 21 patients with chronic cervical pain.^[2]
- In another European study from 2008, Bernateck et al. reported the use of the P-Stim device in a RCT of 44 patients with rheumatoid arthritis.^[3] The control group received autogenic training, a psychological intervention in which participants learn to relax their limbs, breathing, and heart. Electro-acupuncture (continuous stimulation for 48 hours at home) and lessons in autogenic training were performed once weekly for 6 weeks. In addition, the control patients were encouraged to use an audiotape to practice autogenic training every day. The needles and devices were removed after 48 hours. Seven patients withdrew from the study before beginning the intervention; the 37 remaining patients completed the study through 3 months of follow-up. The primary outcome measures were the mean weekly pain intensity and the disease activity score (DAS-28). At the end of treatment and at 3-month follow-up, a statistically significant improvement was observed in all outcome measures for both groups. There was greater improvement in the electro-acupuncture group than the control group (e.g., VAS pain 2.79 vs. 3.95) during the treatment period. This difference did not persist at the 3-month follow-up. The clinical significance of a 1-point difference in VAS from this small trial is unclear.

- A 2011 randomized trial from Europe tested the efficacy of the P-Stim in 40 female patients undergoing gynecologic surgery.^[4] Patients were randomly assigned to receive auricular acupuncture or sham stimulation. Patients in the control group received electrodes without needles and the P-Stim devices were applied without electrical stimulation. The P-Stim device was placed behind the ear at the end of the operation on all patients while they were still under general anesthesia, and the dominant ear was completely covered with identical dressing in both groups to maintain blinding. Postoperatively, patients received 1,000 mg paracetamol every 6 hours, with additional piritramide given on demand. Needles and devices were removed 72 hours postoperatively. A blinded observer found no significant difference between the 2 groups in consumption of piritramide during the first 72 hours postoperatively (acupuncture vs. placebo: 15.3 mg vs. 13.9 mg, respectively) or on VAS scores taken at 0, 2, 24, 48, and 72 hours (average of 2.32 vs. 2.62, acupuncture vs. placebo, respectively). In this small study, use of the P-stim device was not associated with improved pain management following gynecologic surgery, although the study size may have been too small to find differences between groups where they existed.

Clinical Practice Guidelines

There are no evidence-based clinical practice guidelines that recommend the use of auricular electrostimulation devices for any indication.

Summary

The evidence available at this time is insufficient to evaluate the effect of auricular electrostimulation on health outcomes, including acute and chronic pain. Additional randomized studies with a larger number of subjects are needed to evaluate the efficacy of this treatment approach. Therefore, auricular electrostimulation is considered investigational.

REFERENCES

1. Sator-Katzenschlager SM, Scharbert G, Kozek-Langenecker SA, et al. The short- and long-term benefit in chronic low back pain through adjuvant electrical versus manual auricular acupuncture. *Anesth Analg*. 2004 May;98(5):1359-64, table of contents. PMID: 15105215
2. Sator-Katzenschlager SM, Szeles JC, Scharbert G, et al. Electrical stimulation of auricular acupuncture points is more effective than conventional manual auricular acupuncture in chronic cervical pain: a pilot study. *Anesth Analg*. 2003 Nov;97(5):1469-73. PMID: 14570667
3. Bernateck M, Becker M, Schwake C, et al. Adjuvant auricular electroacupuncture and autogenic training in rheumatoid arthritis: a randomized controlled trial. Auricular acupuncture and autogenic training in rheumatoid arthritis. *Forsch Komplementmed*. 2008 Aug;15(4):187-93. PMID: 18787327
4. Holzer A, Leitgeb U, Spacek A, Wenzl R, Herkner H, Kettner S. Auricular acupuncture for postoperative pain after gynecological surgery: a randomized controlled trial. *Minerva Anesthesiol*. 2011 Mar;77(3):298-304. PMID: 21441884

CROSS REFERENCES

None

CODES	NUMBER	DESCRIPTION
CPT	None	
HCPCS	S8930	Electrical stimulation of auricular acupuncture points; each 15 minutes of personal one-on-one contact with the patient

Enzyme Replacement Therapy - Gaucher's Disease

Question:

What should the HERC determine about placement on the Prioritized List for enzyme replacement therapy for Gaucher's Disease?

Question Source:

ICD-10 pediatric metabolic consultants

Dr. Neil Buist, and Dr. Dave Koeller, OHSU

Genzyme pharmaceuticals

Issue:

At the August 2012 VBBS/HERC meetings enzyme replacement therapies (with the exception of infantile Pompe's disease) were included on Line 684, including treatment of Gaucher's disease. At that time, there was no high quality data (Cochrane reviews or randomized controlled trials) identified to support coverage. Those studies that were identified appear to focus on primary endpoints of hemoglobin concentrations and not on patient-oriented outcomes. Since that time, the ICD-10 pediatric metabolic consultants Drs. Buist and Koeller have approached staff with additional evidence and the makers of Cerezyme have also submitted evidence with the request that since this is so rare RCT evidence is not available and case series and registries should be considered.

Clinical Background:

Gaucher disease is characterized by a deficiency of β -glucocerebrosidase activity, resulting in accumulation of glucocerebroside in tissue macrophages which become engorged and are typically found in the liver, spleen, and bone marrow and occasionally in lung, kidney, and intestine. Secondary hematologic sequelae include severe anemia and thrombocytopenia in addition to the characteristic progressive hepatosplenomegaly, skeletal complications, including osteonecrosis and osteopenia with secondary pathological fractures.

Current Prioritized List Status

ICD 9 272.7 Lipoidosis

Line	Condition	Treatment
67	METABOLIC DISORDERS INCLUDING HYPERLIPIDEMIA	MEDICAL THERAPY
78	NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS	MEDICAL AND SURGICAL TREATMENT (EG. G-TUBES, J-TUBES, RESPIRATORS, TRACHEOSTOMY, UROLOGICAL PROCEDURES)
110	END STAGE RENAL DISEASE	RENAL TRANSPLANT
318	NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS	MEDICAL AND SURGICAL TREATMENT (EG. DURABLE MEDICAL EQUIPMENT AND ORTHOPEDIC PROCEDURE)
375	NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS	MEDICAL THERAPY
407	DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF- DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION	MEDICAL THERAPY (SHORT TERM REHABILITATION WITH DEFINED GOALS)
684	ENDOCRINE AND METABOLIC CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY	EVALUATION

ICD-10 E75.22 Gaucher disease

GUIDELINE NOTE 67, ENZYME REPLACEMENT THERAPY

Lines 264,684

Enzyme replacement therapy for infantile Pompe's disease is included on Line 264. All other enzyme replacement therapies are included on Line 684.

Evidence summary

Previous searches:

Cochrane – nothing

NICE – nothing

BMJ clinical evidence – nothing

There have been no randomized controlled trials comparing treatment to placebo or standard care. There has been one RCT done on this subject, but only examined comparative effectiveness of one enzyme replacement to another (Cerezyme to Ceredase) without a placebo control.

Submitted studies reviewed

Barton, 1991 – original FDA qualifying study

1. N = 12 patients, 4 adults and 8 children
2. Type of study – case series
3. Injections q1-2weeks for 9-12 months
4. Results:
 - a. Hemoglobin concentration increased in 12/12, and platelet count in 7/12
 - b. Splenic volume decreased in 12/12 and hepatic volume in 5/12
 - c. Improvement in biochemical markers
 - d. “all children gained weight during the study and all children grew taller.”
 - e. Subjective improvements in quality of life

Charrow, 2007

1. Registry study
2. Population defined as those with bone crisis the year before therapy
3. Bone crises are based on physician reports
4. Results: Following ERT treatment, the percentage of positive bone pain responses per patient declined to 30%, 29%, and 30% in the first, second and third years on ERT, respectively. These represent 38%, 40%, and 39% declines in the percentage of bone pain responses per patient compared to before treatment (p,0.0001 for each year post-ERT).
5. After starting ERT, the percentage of patients with bone crisis reports decreased significantly to 5%, ,1%, and 3% of patients in the first, second and third years of therapy, respectively

Ficicioglu, 2008

1. Clinical review of miglustat (substrate reduction therapy)
2. No methodology identified
3. 6-36 month results show improvements in bone pain, improvements in hemoglobin and platelet concentrations. Efficacy of miglustat may be comparable to enzyme replacement therapy
4. Adverse effects are significant, such as diarrhea and bloating, tremor, and peripheral neuropathy
5. Approved in the US for those in whom ERT is not an option

Masek, 1999

1. Prospective cohort study of Ceredase
2. Evaluated Quality of Life using standard questionnaire, up to 2 years
3. N= 25 adults
4. Results:

- a. At 6 months, energy level and fatigue was improved (compared to baseline), and improvement in 7/8 scores by 18 months.

Pastores, 2011

1. Clinical review of Gaucher's disease
2. No methodology identified
3. Other types of symptomatic therapy include:
 - a. Miglustat - resulted
 - i. Significant decrease in liver and spleen volume after six to 18 months, with clinical improvement noted over 24 months.
 - ii. Bone involvement and platelet and hemoglobin values remained stable or were modestly improved [Cox et al 2000, Elstein et al 2004a, Pastores et al 2005].
 - iii. An increase in bone density at the lumbar spine and femoral neck was reported to occur as early as six months after the initiation of miglustat monotherapy [Pastores et al 2007].
 - iv. Adverse effects: The most common adverse reactions noted in the clinical trials were weight loss (60% of individuals), and bloating, flatulence, and diarrhea (80%), which resolved or diminished with longer use of the product.
 - b. Partial or total splenectomy
 - c. Transfusion of blood products
 - d. Analgesics for bone pain
 - e. Joint replacement surgery
 - f. Supplemental calcium, vitamin d, and bisphosphanates

Sims, 2008

1. 48 month, open-label, longitudinal cohort study
2. Comparison was baseline, no control group
3. Improvements in bone pain, bone mineral density, and bone crisis at 3 months

Weinrub, 2002

1. Registry study
2. N=1028 patients
3. Results:
 - a. Hemoglobin levels improved (most in the first 6 months of treatment)
 - b. Hepatomegaly decreased by 30-40%
 - c. Splenomegaly decreased by 40-50% (but still remained at least 5x normal size)
 - d. In patients with pretreatment bone pain or bone crises, 52% (67/128) were pain free after 2 years and 94% (48/51) reported no additional crises.
4. Considerations: this is registry data so follow up may be limited in those with differing results. No comparison between those receiving therapy and not receiving therapy.

Wenstrup, 2007

1. Comparative cohort study between non-ERT and ERT treated patients
2. Non ERT (N=160) and ERT treatment (N=342 patients)
3. All registry patients with lumbar spine DEXA scores available
4. Considerations: The no ERT group tended to be less severe overall as evidenced by higher baseline hemoglobin and platelet counts, lower spleen and liver volumes, and lower presence of bone pain and occurrence of bone crisis. At baseline both significantly worse than standard population and possibly significantly different from each other
5. Results: Dose response relationship was present with ERT and improvement in bone density
6. Although they obtained baseline bone pain and bone crisis data, this was not followed up (or reported on)
7. May take up to 8 years to see effects

Zimran, 2010

1. Open label case series, Velaglucerase alfa
2. 12 patients, 9/12 completed 39 months.
3. Evaluated at 9 months and 48 months
4. Results improvements at 9 and 48 months:
 - a. Hemoglobin increased (19.2% and 21.7%)
 - b. Platelet counts increased (67% and 158%)
 - c. Normalized liver volume (-18.2%, -42.8%)
 - d. Normalized spleen volume (-49.5%, -79.3%)

Commerical Plans

Aetna, 2012

Alglucerase (Ceredase), Imiglucerase (Cerezyme), Miglustat (Zavesca), Taliglucerase alfa (Eleyso), and Velaglucerase Alfa (VPRIV)

Aetna considers alglucerase (Ceredase), imiglucerase (Cerezyme), miglustat (Zavesca), taliglucerase alfa (Eleyso), and velaglucerase alfa (VPRIV) medically necessary for adult members with Type 1 Gaucher disease who have any of the following signs and symptoms:

- Moderate to severe anemia (hemoglobin less than or equal to 11.5 g/dL (adult women) or 12.5 g/dL (adult men) or less than or equal to 1.0 g/dL or more below the lower limit of normal for age and sex); or
- Significant hepatomegaly (liver size 1.25 or more times normal (1,750 cc in adults)) or splenomegaly (spleen size 5 or more times normal (875 cc in adults)); or
- Skeletal disease beyond mild osteopenia and Erlenmeyer flask deformity; or
- Symptomatic disease, including abdominal or bone pain, fatigue, exertional limitation, weakness, or cachexia; or
- Thrombocytopenia (platelet count less than or equal to 120,000/mm³).

Aetna considers alglucerase, imiglucerase, miglustat, taliglucerase alfa, and velaglucerase alfa medically necessary for children and adolescents less than 18 years of age who are diagnosed with Type 1 Gaucher disease.

Aetna considers alglucerase, imiglucerase, miglustat, taliglucerase alfa, and velaglucerase alfa experimental and investigational for all other indications because of insufficient evidence in the peer-reviewed literature.

This policy is based, in part, on the recommendations of the International Collaborative Gaucher Group U.S. Regional Coordinators and the National Institutes of Health Technology Assessment Conference on Gaucher Disease.

Cigna, 2012

Cigna covers the following long-term enzyme replacement therapies as medically necessary for Type 1 Gaucher disease:

- imiglucerase (Cerezyme®)
- taliglucerase alfa (Elelyso™)
- velaglucerase alfa (VPRIV™)

Cigna covers miglustat (Zavesca®) as medically necessary for the treatment of mild to moderate Type 1 Gaucher disease in adults for whom enzyme replacement therapy is not a therapeutic option.

When coverage is available and medically necessary, the dosage, frequency, site of administration, and duration of enzyme replacement therapy should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to enzyme replacement therapy.

Health Partners, 2011

Enzyme replacement therapy for Gaucher's disease is considered medically necessary for pediatric and adult patients with a confirmed diagnosis of Type I Gaucher disease resulting in one or more of the following conditions: moderate to severe anemia, thrombocytopenia with bleeding tendency, bone disease, significant hepatomegaly or splenomegaly.

The labeled dosage is 60 units/kg administered every other week as a 60-minute intravenous infusion. However, after therapeutic goals are achieved, the lowest effective dose should be used.

Annual reauthorizations will require (1) a statement of progress against therapy goals which should include assessments of hemoglobin, platelet count, and liver and/or spleen volumes by MRI (when MRI is clinically indicated); and (2) for all regimens using more than 30 units/kg every other week, a statement of medical necessity indicating that the lowest effective dose to maintain therapeutic goals is being used.

Cost information

Based on a recommended dosing of 60U/kg every 2 weeks, the monthly cost for a 100kg person would be \$50,088. This translates to an annual cost of \$601,056.

Summary

There are no high quality studies to support the use of enzyme replacement therapy for Gaucher Type 1. There are case series and cohort studies without controls that demonstrate improvements in hemoglobin, platelets, spleen size, liver size, bone density, bone crises, and bone pain. There is a single comparative study that found improvement in bone mineral density at 8 years. There is no data available about patients who discontinue therapy or who choose not to be on therapy compared to those remaining on therapy. This comparative data would be possible to obtain from the registry. There no evidence to show that ongoing treatment with ERT prevents long-term clinical complications (e.g. infection, hospitalization, and mortality).

HERC Staff Recommendation

1. **Option 1:** Make no change. Await comparative data to demonstrate efficacy on patient-oriented outcomes.
2. **Option 2:** If the decision is made to prioritize this therapy higher, Guideline Note 67 would need to be modified as follows:

GUIDELINE NOTE 67, ENZYME REPLACEMENT THERAPY

Lines [67](#), [264](#),[684](#)

Enzyme replacement therapy for [Type 1 Gaucher disease is included on Line 67 and for](#) infantile Pompe's disease is included on Line 264. All other enzyme replacement therapies are included on Line 684.

Consider adding this additional wording to the guideline:

Enzyme replacement therapy is only included on Line 67 for Type 1 Gaucher's disease in adults when at least two or three of the following criteria are met:

- Moderate to severe anemia (hemoglobin less than or equal to 11.5 g/dL (adult women) or 12.5 g/dL (adult men) or less than or equal to 1.0 g/dL or more below the lower limit of normal for age and sex); or
- Significant hepatomegaly (liver size 1.25 or more times normal (1,750 cc in adults)) or splenomegaly (spleen size 5 or more times normal (875 cc in adults)); or
- Skeletal disease beyond mild osteopenia and Erlenmeyer flask deformity; or

- Symptomatic disease, including abdominal or bone pain, fatigue, exertional limitation, weakness, or cachexia; or
- Thrombocytopenia (platelet count less than or equal to 120,000/mm³) with bleeding history

For children and adolescents with Type 1 Gaucher's disease, the above criteria do not need to be met, they simply must be symptomatic.

For all recipients of enzyme replacement therapy there needs to be documentation of responsiveness to the enzyme replacement therapy and the lowest effective dose should be used in order for continued coverage.

OVERVIEW OF SUBMISSION

This package contains in-depth information on Gaucher disease, one of the lysosomal storage disorders (LSDs), and Cerezyme® (imiglucerase for injection), an enzyme replacement therapy (ERT) used to treat Gaucher disease. Ceredase® (alglucerase injection), a biologically derived ERT for the treatment of Gaucher disease received FDA approval in 1991. Cerezyme, the recombinant form of this therapy was approved by the FDA in 1994 and is the current ERT for the treatment of Gaucher disease manufactured by Genzyme, A Sanofi Company.

This submission includes background information on LSDs in general. The appendices contain a copy of the full prescribing information for Cerezyme. We have also included a diagnostic code and billing table for your information.

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1. INTRODUCTION TO LYSOSOMAL STORAGE DISORDERS

Lysosomes are membrane-bound organelles that contain numerous acid hydrolases whose function is to catabolize a wide range of macromolecules including lipids, proteins and complex carbohydrates¹. They play a critical role in the normal cellular metabolism, protein localization, membrane transport, development and cell intercommunication.¹ If there is an absence or defective function of one of these enzymes, there is a bottleneck in the catabolic pathway leading to progressive accumulation of specific macromolecules. This progressive accumulation of substrate eventually interferes with cellular function.¹ Lysosomal storage disorders (LSDs) include over 40 monogenic inherited disorders that are a consequence of a deficiency of a single enzyme or protein.¹ The genetic causes of most have been identified. Currently no definitive genotype-phenotype correlation has been demonstrated in most LSDs and therefore genotype often does not predict the clinical course of the disease nor does residual enzyme activity levels.²

LSDs are all extremely rare and are part of a larger category called “orphan diseases”. Orphan diseases are defined as conditions affecting fewer than 200,000 patients.³ The collective prevalence of LSDs has been estimated at 1 in 7700 individuals.⁴ LSDs differ from each other by a number of variables including the underlying genetic defect, the associated enzyme deficiency, the substrate stored and the cell types affected. Because of this, LSDs encompass remarkable heterogeneity.² Given how rare these disorders occur, the pathophysiology and natural history is often not well understood. Longitudinal data collection in disease registries for a subset of disorders has greatly helped to more clearly delineate the natural histories, although questions still remain.

Research has led to various disease-specific approaches for the delivery of endogenous or exogenous lysosomal enzymes to targeted tissues via the bloodstream. Enzyme replacement therapy (ERT) provides the deficient enzyme exogenously and is currently available for 6 LSDs: Gaucher disease, Fabry disease, Pompe disease, and Mucopolysaccharidosis types I, II and VI. Other therapeutic approaches currently used or under exploration in some LSDs include hematopoietic stem cell transplantation (which provides matched donor hematopoietic

stem cells that can produce the missing enzyme), gene therapy, chaperone therapy and substrate reduction therapy.¹

2. GAUCHER DISEASE

a. OVERVIEW

Gaucher disease is a lysosomal glycolipid storage disorder that results from a deficiency in activity of the lysosomal enzyme glucocerebrosidase (acid β -glucosidase). This enzyme deficiency leads to the accumulation of its substrate, glucosylceramide (glucocerebroside) in cells derived from the monocyte/macrophage system.⁵ Thus, Gaucher disease is an inherited metabolic disease that primarily affects organs where tissue macrophages are prevalent.

b. EPIDEMIOLOGY AND INHERITANCE

Published estimates of the incidence of Gaucher disease range from 1 in 40,000 to 1 in 60,000.^{4,6,7} The estimated prevalence of symptomatic patients in the United States is less than 3,000.⁶ Gaucher disease is inherited in an autosomal recessive fashion and affects both males and females.⁵

Three subtypes of Gaucher disease are commonly recognized: type 1 (non-neuronopathic), type 2 (acute neuronopathic), and type 3 (chronic neuronopathic). Type 1 is by far the most common type, representing approximately 94% of the total Gaucher disease population.⁸ Onset of clinically evident signs and symptoms in type 1 Gaucher disease can occur in childhood or late into adulthood. Onset of type 2 and type 3 occurs in infancy and childhood respectively. Patients with type 2 disease, which is characterized by severe and rapidly progressive neurological and cutaneous symptoms, usually die before 2 years of age. Patients with type 3 disease are more slowly progressive and characteristically have ophthalmologic and developmental central nervous system manifestations. Type 3 patients commonly live into their second to fourth decades of life.⁵

The focus of this clinical submission is on Gaucher disease type 1.

c. PATHOPHYSIOLOGY

Gaucher disease is caused by mutations in the acid β -glucosidase gene, GBA. Over 300 different pathological mutations have been identified to date.⁶ A mutation in the GBA gene impacts the production or enzymatic activity of glucocerebrosidase and leads to progressive accumulation of the substrate, glucosylceramide. The hallmark of untreated Gaucher disease type 1 is the accumulation of lipid-engorged cells primarily in the liver, spleen, and bone marrow and secondarily in the lungs, kidneys and intestines.⁵ Gaucher disease exhibits extreme phenotypic heterogeneity even among individuals with the same genotype.⁶

d. DISEASE MANIFESTATIONS

i. Natural History

The natural history of this disorder has been more fully delineated through the International Collaborative Gaucher Group (ICGG) Gaucher Registry. The ICGG Gaucher Registry was established in 1991. As of 2012, approximately 6000 patients have been enrolled at more than 400 sites globally. A number of clinical features of Gaucher disease have been elucidated as a result of data collected in the ICGG Gaucher Registry.⁹

The natural history can differ between patients with Gaucher disease type 1 in terms of age of presentation, cluster of presenting symptoms, disease progression and co-morbidities. Symptoms of Gaucher disease type 1 can present in childhood through adulthood. Signs and symptoms of Gaucher disease type 1 that manifest during the first and second decade of life are usually indicative of more rapidly progressive disease compared with disease that is diagnosed later in life.^{5, 24} Survival in Gaucher disease type 1 ranges from 6 to 80+ years.⁵

ii. Primary Clinical Manifestations

The most common clinical manifestations of Gaucher disease type 1 include hematologic, visceral and bone symptoms.

Hematologic manifestations

Anemia (low hemoglobin level) and thrombocytopenia (low platelet count) are the most common hematologic manifestations of Gaucher disease. Severe anemia (hemoglobin level ≤ 10 g/dL) or moderate anemia (hemoglobin level between 10 g/dL and <12 g/dL) was found in 69% of patients with intact spleens in a study from the ICGG Gaucher Registry.⁸ Anemia is a major cause of fatigue in Gaucher patients. Thrombocytopenia which may be found in combination with coagulopathies, leads to easy bruising and excessive bleeding; in patients with severe thrombocytopenia, bleeding events can be life-threatening. Seventy-six percent of patients with intact spleen and 13% of splenectomized patients in the ICGG Gaucher Registry presented with moderate thrombocytopenia (platelet count 60,00/mm³ to $\leq 120,000$ /mm³) to severe thrombocytopenia (platelet count $\leq 60,000$ /mm³).⁸

Visceral manifestations

The accumulation of Gaucher cells in spleen and liver can lead to massive hepatosplenomegaly. In patients with Gaucher disease type 1, a diseased spleen can be up to 70 times its normal volume and the liver can be up to 10 times its normal volume.⁵ This organomegaly can lead to secondary consequences such as decreased appetite, poor nutrient absorption and cachexia. A study of 1,698 patient with Gaucher disease enrolled in the ICGG disease registry found that 50% had spleen volumes more than 15 times normal and 37% had spleen volumes 5-15 times normal.⁸ Seventy-nine

percent of patients had liver volumes at least 1.25 times normal, including 23% with liver volumes more than 2.5 times normal.⁸

Bone manifestations

While hematologic and visceral symptoms are often the most obvious manifestations of Gaucher disease, bone symptoms are typically the most debilitating. Bone disease is generally progressive and over 80% of patients with Gaucher disease have bone involvement at the time of diagnosis (Table 1).⁸ Bone symptoms include bone pain, osteoporosis, necrosis and loss of cortical bone. The most prevalent bone abnormality is a failure of the distal femur and the proximal tibia to remodel correctly, resulting in the classic “Erlenmeyer flask” appearance; this generally does not cause symptoms. Bone pain has been reported in up to one-third of patients at the time of diagnosis.⁸ Osteopenia is also common and is often found in pediatric as well as young adult patients. Severe bone manifestations such as lytic lesions, infarcts, avascular necrosis, fractures and joint collapse are less common but are severely painful and often incapacitating.

Table 1. Bone Manifestations at Time of Diagnosis* for Patients With Gaucher Disease (All Types)

Bone Pain, n (%)		n=1416
Absent		934 (66%)
Present		482 (34%)
Very Mild		57 (12%)
Mild		125 (26%)
Moderate		93 (19%)
Severe/Extreme		48 (10%)
Not Specified		159 (33%)
Prior Bone Crisis, n (%)		n=1361
Absent		1258 (92%)
Present		103 (8%)
Radiologic Bone Disease, n (%)		n=1046
Evidence of Any Bone Disease		
Absent		184 (18%)
Present		862 (82%)
Type of Bone Disease Reported	Any Data Available, n	Type of Bone Disease Reported
Avascular Necrosis	550	90 (16%)
Erlenmeyer Flask Deformity	644	378 (59%)
Fractures	441	33 (7%)
Infarction	524	122 (23%)

Lytic Lesions	444	81 (18%)
Marrow Infiltration	617	499 (81%)
Osteopenia	541	279 (52%)

Decreased Bone Mineral Density (lumbar spine DXA z-score[†]), n (%)	n=265	
Mild or None (> -1)	142	(54%)
Moderate (> -2.5 to ≤ -1)	93	(35%)
Severe (≤ -2.5)	30	(11%)

Pediatric Growth Retardation, n (%)	n=881	
Observed	314	(36%)
Expected [‡]	44	(5%)

* "At the time of diagnosis" is defined as the data point closest to the diagnosis date, no more than ± 2 years from diagnosis, and before any initiation of imiglucerase therapy. Patients with no diagnosis or with diagnosis date earlier than 1 year prior to their birth and for patients with no infusion date were excluded from the analysis for each bone assessment.

† Standard deviations of age and sex-adjusted norms.

‡ Pediatric growth retardation is defined as the number of patients are below the 5th percentile for height based on age and gender of the normal healthy population and is calculated as 0.05 X total number of patients (Kuczumski RJ, Ogden CL, Grummer-Strawn LM et al. CDC growth charts

Source: ICGG Gaucher Registry 2009 Annual Report, Genzyme Corporation on file

iii. Pediatric manifestations

Approximately two-thirds of patients with symptomatic Gaucher disease type 1 have disease manifestations in childhood.¹⁰ Early symptoms are associated with the development of more severe manifestations. A report from the ICGG registry of 887 untreated children younger than 18 years of age with Gaucher disease type 1 showed that 34% had growth retardation, 87% had hepatomegaly, 95% had splenomegaly, 40% had anemia, 50% had thrombocytopenia, and 91% had radiologic evidence of bone disease.¹⁰ Older children tend to have significantly more severe skeletal manifestations than younger children; this may be related to the slower progression of skeletal disease or to the stress put on bone growth and remodeling during and after puberty. Children with untreated Gaucher commonly have retarded growth and have also have delayed puberty.¹⁰

iv. Associated Clinical Co-morbidities

Patients with Gaucher disease may also be at increased risk for co-morbidities, including pulmonary hypertension, multiple myeloma and Parkinson disease.

Pulmonary hypertension

Individual case reports have described glycolipid-laden macrophages lining the pulmonary capillaries, resulting in pulmonary hypertension with classic plexogenic vasculopathy. The prevalence of mild pulmonary hypertension in patients with Gaucher disease type 1 has been reported to be as high as 30%.¹⁰ Asplenic patients appear to be at higher risk primarily due to the higher migration of lipid-laden macrophages to the liver, skeleton and to lung tissue.¹¹

Multiple Myeloma

Patients with Gaucher disease type 1 are at an increased risk for developing multiple myeloma; recent estimates of the risk relative to population norms range from a 6-fold to 50-fold increase.^{12, 13, 14} Gaucher has also been associated with both monoclonal and polyclonal gammopathies. Monoclonal gammopathy may precede multiple myeloma.¹²

Parkinson Disease

Single mutations in the GBA gene have now been established as a major genetic risk factor for developing Parkinson disease; however it is not yet clear to what degree Parkinson disease incidence is elevated in the Gaucher population, nor what is the underlying mechanism for this increased risk.^{15,16}

e. DIAGNOSIS

Gaucher disease is usually suspected based on clinical presentation (often including unexplained bone pain, hepatosplenomegaly, or hematologic abnormalities) or family history. The diagnosis of Gaucher disease is made by demonstration of decreased acid β -glucosidase activity in peripheral blood leukocytes or cultured skin fibroblasts (<30% of normal activity).¹ Demonstration of two mutant alleles of the GBA gene provides diagnostic verification.¹

3. CERZYME TREATMENT

a. OVERVIEW

Prior to the advent of enzyme replacement therapy (ERT), the treatment of Gaucher disease was limited to symptomatic care and treatment to address anemia, hypersplenism (splenectomy), bone pain, osteopenia/osteoporosis and other bone manifestations (surgical joint replacement, analgesics, etc). These interventions fail to address the underlying pathology of Gaucher disease type 1 and in the case of splenectomy can lead to additional disease complications.¹⁷ In contrast, ERT provides an exogenous source of glucocerebrosidase that is targeted to the lysosome and breaks down the accumulated substrate. The first ERT for Gaucher disease, Ceredase® (alglucerase injection), was derived from placental tissue. Ceredase was approved by the FDA in 1991. A recombinant form of glucocerebrosidase, Cerezyme® (imiglucerase for injection), was developed and approved by the FDA in 1994.



Enzyme replacement therapy is the accepted standard of treatment for symptomatic patients with Gaucher disease type 1. Cerezyme has been proven to be both safe and highly effective. Cerezyme has been shown to significantly improve visceral, hematologic and skeletal signs and symptoms of Gaucher disease type 1 in both adult and pediatric patients.^{18,19,20, 22, 23}

i. Indication

Cerezyme is indicated for long-term enzyme replacement therapy for pediatric and adult patients with a confirmed diagnosis of Gaucher disease type 1 that results in one or more of the following conditions:²¹

- a. anemia
- b. thrombocytopenia
- c. bone disease
- d. hepatomegaly or splenomegaly

The FDA approval for this indication was granted in May 1994.

ii. Safety information

Table 2 includes adverse event information. Experience in patients treated with Cerezyme shows that approximately 13.8% of patients experienced adverse events that were judged to be related to Cerezyme administration and that occurred with an increase in frequency. Symptoms suggestive of hypersensitivity have been noted in approximately 6.6% of patients. Anaphylactoid reaction has also been reported in <1.5% of the total patient population. Additional adverse reactions have been reported in approximately 6.5% of the population each with an incidence of less than 1.5% each.²¹

Approximately 15% of patients have developed IgG antibodies, and these patients have a higher risk of hypersensitivity reaction. Therefore periodic monitoring is suggested; caution should be exercised in patients with antibodies or prior symptoms of hypersensitivity.²¹

The long term safety of Cerezyme has been demonstrated.²⁰ Since the approval of Cerezyme in May 1994, Genzyme has maintained a worldwide post marketing database of spontaneously reported adverse events and adverse events discussed in the medical literature. International safety data compiled between 1997 and 2004 reveal the majority of patients have tolerated 1- to 2-hour infusions of Cerezyme without the development of adverse events and have been treated with Cerezyme for up to 10 years without any evidence of long-term toxicity.²⁰ A review of accumulated safety data, including more than 10 years of immunosurveillance experience has not identified any new significant safety concerns about the use of Cerezyme in patients with Gaucher disease.²⁰

Table 2. Adverse Events Associated With Cerezyme²¹

Associated with Route of Administration (Incidence <1% each)	Suggestive of Hypersensitivity (Incidence <1.5% each)	Additional Events (Incidence <1.5% each)
<ul style="list-style-type: none"> ◆ Discomfort ◆ Pruritus ◆ Burning ◆ Swelling ◆ Sterile abscess at the site of venipuncture 	<ul style="list-style-type: none"> ◆ Anaphylactoid reaction ◆ Pruritus ◆ Flushing ◆ Urticaria ◆ Angioedema ◆ Chest discomfort ◆ Dyspnea ◆ Coughing ◆ Cyanosis ◆ Hypotension 	<ul style="list-style-type: none"> ◆ Nausea ◆ Vomiting ◆ Abdominal pain ◆ Diarrhea ◆ Rash ◆ Fatigue ◆ Headache ◆ Fever ◆ Dizziness ◆ Chills ◆ Backache ◆ Tachycardia

b. OUTCOME DATA AND SUPPORTING CLINICAL EVIDENCE

i. Original Treatment Study

Ceredase Pivotal Trial

The original pivotal trial showed the impact of Ceredase on Gaucher disease type 1.²²

- Splenic and hepatic volumes decreased in all patients within 6 months. No antibodies to Ceredase were developed during the trial.
- Hemoglobin levels increased significantly.
- Infusions were well tolerated, and side effects were minimal.
- Quality of life improved (patient assessment).

ii. Randomized Controlled Study

Cerezyme Pivotal Trial: Ceredase Versus Cerezyme Comparative Efficacy Study

A double-blind, randomized, parallel-group trial established that there are no significant clinical differences between Ceredase and Cerezyme.²³

- There were no significant differences in hepatic or splenic volume changes between the Cerezyme and Ceredase groups.
- Therapeutic response to Cerezyme was not diminished because of anti-glucocerebrosidase antibody development.

iii. Open Label Study

Skeletal Response

1) A prospective, nonrandomized, open-label study of 33 Cerezyme- or Ceredase-naïve patients with skeletal manifestations of Gaucher disease type 1 found the following:²⁵

- Cerezyme treatment significantly reduced bone pain after 3 months of therapy, and this effect was sustained throughout the rest of the 4-year observational period.
- Lumbar spine bone mineral density (BMD) significantly improved after 24 months of Cerezyme therapy and continued to improve thereafter, reaching near-normal levels at 48 months.
- Femoral neck BMD increased significantly after 36 months of Cerezyme therapy.

iv. Registry Data

As mentioned earlier in this document, the ICGG Gaucher Registry was established in 1991 by the International Collaborative Gaucher Group to longitudinally track the clinical assessments and clinical outcomes of patients with Gaucher disease, irrespective of treatment status. The ICGG Gaucher Registry is supported by Genzyme Corporation and governed by an international group of physician advisors. It is the largest observational registry for Gaucher disease in the world and currently includes data on more than 6,000 patients from more than 60 countries. The data collected include demographic variables, disease characteristics (including genotype, spleen status, hematologic parameters, liver function data, and liver and spleen volumes), clinical and radiologic assessments of skeletal involvement, quality of life measures and therapeutic goals.

Analyses of ICGG Gaucher Registry data provide valuable information that can be applied to optimizing disease management. This information has included:^{18, 8, 19}

- Ongoing insight into the Gaucher disease process
- Demographics and disease characteristics
- The effects of Cerezyme on various clinical manifestations of Gaucher disease
- Assessment of success in achieving and maintaining established therapeutic goals

Large, randomized, controlled clinical studies in rare diseases are difficult to conduct; the ICGG Gaucher Registry provides an alternative source of data for evidence-based decision-making for individual physicians and managed care organizations. From 1991 through 2009, ICGG Gaucher Registry data have made possible 31 peer-reviewed publications on Gaucher disease, including 15 papers analyzing the natural history of the disease and 16 papers considering the observed effects of enzyme replacement therapy with Ceredase and Cerezyme.

Effectiveness of Long-term Enzyme Replacement Therapy

1) An analysis of long-term (2 to 5 years) effects of treatment with Ceredase or Cerezyme based on 1,028 patients in the observational ICGG Gaucher Registry found the following:¹⁸

- 82% of patients with a history of bone crises reported none within the first year of treatment.
- Splenomegaly decreased by 50% to 60% during the 5-year follow-up period.

- Hepatomegaly decreased by 30% to 40% during the 5-year follow-up period.
- Improvements in hemoglobin levels, platelet counts, and liver and spleen volumes were sustained after 3 to 5 years of treatment.

2) A recent analysis of 757 patients at baseline and after 10 years of ERT in patients enrolled in the ICGG Gaucher Registry showed improvements across disease parameters including: ²⁶

- Sustained increases in hemoglobin level and platelet count
- Sustained decreases in liver and spleen volumes
- Improvements seen in both splenectomized and non-splenectomized patients.

Skeletal Response

1) A retrospective analysis of the effects of treatment with Cerezyme (n=342), compared with no treatment (n=160), over an 8-year observational period found the following: ²⁷

- Treatment with Cerezyme 60 U/kg every 2 weeks resulted in a significant increase in lumbar spine BMD over time
- Mean BMD levels approached the mean value for the normal healthy population after 8 years of treatment.
- Increases in lumbar spine BMD were dose-dependent.

2) A retrospective analysis of patients with Gaucher disease type 1 who had bone pain (n=244) or bone crisis (n=219) before Cerezyme/Ceredase treatment found the following: ²⁸

- Cerezyme or Ceredase treatment significantly reduced the frequency of bone pain and bone crisis during each of 3 years of treatment compared with the pretreatment frequency.
- The frequency of bone crisis was significantly reduced from 17% before treatment to 5%, <1%, and 3% in the first, second, and third year of Cerezyme or Ceredase treatment, respectively.
- The frequency of bone pain decreased from 49% before treatment to 30%, 29%, and 30% in the first, second, and third years of Cerezyme or Ceredase treatment, respectively. No significant differences were seen between the two treatments.

3) A retrospective analysis of 2,700 patients enrolled in the Gaucher registry who were not diagnosed with avascular necrosis (AVN) prior to inclusion were included in a study to determine whether the time from diagnosis to initiation of treatment with Cerezyme influenced the rate of avascular necrosis in these patients. ²⁹

- An incidence rate of 13.8 per 1,000 person years was observed in patients not receiving ERT
- In patients receiving enzyme replacement therapy with imiglucerase, an incidence rate of 8.1 per 1,000 person years was observed
- In contrast, an AVN incidence rate of 16.6 per 1,000 person years was observed in patients who initiated therapy greater than two years after initial diagnosis

- The adjusted incidence ratio in the treated group overall was 0.59

Pediatric data

1) A study from the ICGG Gaucher Registry analyzed clinical responses to long-term Ceredase or Cerezyme treatment (8 years) for 884 children with Gaucher disease type 1 found the following:³⁰

- Visceral: Liver and spleen volumes decreased from 2.0 and 23 multiples of normal, respectively, at baseline to near-normal or normal volumes in all children after 8 years of Ceredase or Cerezyme treatment.
- Hematologic
 - Median normalized hemoglobin values improved from -0.3 g/dL at baseline to +1.7 g/dL, and anemia resolved in all patients after 8 years of treatment.
 - Median platelet count improved from $98 \times 10^3/\text{mm}^3$ at baseline to $171 \times 10^3/\text{mm}^3$ after 8 years of treatment.
- Growth Acceleration:
 - Median height approximated the median for the normal population after 8 years of treatment (at baseline, 42% of 702 evaluable patients were below the fifth percentile)
- Skeletal Response:
 - Median BMD z-score value normalized within 6.6 years of treatment.
 - 17% of patients reported a bone crisis before treatment and during the first 2 years of treatment, but after 2 years of Ceredase or Cerezyme treatment, no bone crises were reported.

c. THERAPEUTIC GOALS

Due to its heterogeneity, the management of Gaucher disease requires an individualized approach to treatment that takes into consideration the patient's disease manifestations and disease burden as well as quality of life needs.^{31,32} Physicians from the ICGG who are expert in the management of patients with Gaucher disease, have developed a disease management algorithm that includes evaluation and monitoring guidelines, evidence based therapeutic goals and guidelines for individualized dosing.

Ideally, patients with Gaucher disease can be enrolled in the ICGG Registry to track therapeutic goals and patient outcomes and benchmark against aggregate patient data. Key therapeutic goals are listed in the table 3. Monitoring guidelines are provided in Appendix B.

Table 3. Key Therapeutic Goals for 12 to 24 Months after Starting Treatment with Cerezyme

Skeletal

No bone crisis

No to very mild bone pain

Hematologic

Hemoglobin

≥11g/dL (females & children)

≥12 g/dL (males)

Platelets

>120,000/mm³

Visceral

Spleen volume ≤ 8 MN

Liver volume ≤ 1.5 MN

Quality of Life (QoL): Improve validated QoL scores within 2-3 years

Adapted from Pastores et al. 2004³¹

4. SUMMARY

Gaucher disease is a lysosomal glycolipid storage disorder that results from a deficiency in activity of the lysosomal enzyme glucocerebrosidase and resulting accumulation of the substrate glucosylceramide. Clinical manifestations include serious hematologic and visceral complications and debilitating bone disease. Gaucher disease is highly variable in presentation and age of onset. Earlier onset, especially in children, is associated with a more severe course of disease.

Enzyme replacement therapy for Gaucher disease provides an exogenous source of the missing enzyme. Cerezyme is a recombinant ERT manufactured by Genzyme, a Sanofi Company. Expected outcomes of ERT with Cerezyme in adult and pediatric patients with Gaucher disease type 1 include:

- decreased hepatomegaly and splenomegaly^{18,30}
- normalization of hemoglobin levels and reversal of anemia in most patients^{18,26,30}
- reversal of thrombocytopenia to levels sufficient to prevent bleeding (reduced clotting)^{18,30}
- reduction in bone marrow infiltration^{33,34,35}
- Reduction in frequency of bone crises and bone pain^{18,25,28,30}
- improvement in bone mineral density (BMD) (lumbar spine and femoral neck)^{25,27,30}
- acceleration of growth in growth-retarded children³⁰
- attainment of normal height in most children after 8 years of treatment³⁰
- Improvement of health-related quality of life^{36,37}
- Low incidence of treatment-related or treatment-limiting adverse events²⁰
- Low rate of formation of IgG antibody to imiglucerase (~15%)²⁰

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6. APPENDICES

Appendix A: Cerezyme Full Prescribing Information

Appendix B: ICGG Gaucher Registry Minimum Recommendations for Monitoring Patients with Nonneuronopathic (Type1) Gaucher Disease

Appendix C: Billing and ICD-9 Codes

REPLACEMENT THERAPY FOR INHERITED ENZYME DEFICIENCY — MACROPHAGE-TARGETED GLUCOCEREBROSIDASE FOR GAUCHER'S DISEASE

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Abstract Background and Methods. Gaucher's disease, the most prevalent of the sphingolipid storage disorders, is caused by a deficiency of the enzyme glucocerebrosidase (glucosylceramidase). Enzyme replacement was proposed as a therapeutic strategy for this disorder in 1966. To assess the clinical effectiveness of this approach, we infused macrophage-targeted human placental glucocerebrosidase (60 IU per kilogram of body weight every 2 weeks for 9 to 12 months) into 12 patients with type 1 Gaucher's disease who had intact spleens. The frequency of infusions was increased to once a week in two patients (children) during part of the trial because they had clinically aggressive disease.

Results. The hemoglobin concentration increased in

all 12 patients, and the platelet count in 7. Serum acid phosphatase activity decreased in 10 patients during the trial, and the plasma glucocerebrosidase level in 9. Splenic volume decreased in all patients after six months of treatment, and hepatic volume in five. Early signs of skeletal improvements were seen in three patients. The enzyme infusions were well tolerated, and no antibody to the exogenous enzyme developed.

Conclusions. Intravenous administration of macrophage-targeted glucocerebrosidase produces objective clinical improvement in patients with type 1 Gaucher's disease. The hematologic and visceral responses to enzyme replacement develop more rapidly than the skeletal response. (N Engl J Med 1991; 324:1464-70.)

GAUCHER'S disease is the most prevalent lysosomal storage disorder. It is caused by an insufficiency of glucocerebrosidase (glucosylceramidase) activity^{1,2} with secondary accumulation of glucocerebrosidase within the lysosomes of macrophages. The storage disorder produces a multisystem disease characterized by progressive visceral enlargement and gradual replacement of the bone marrow with lipid-laden macrophages. Symptomatic anemia, coagulation abnormalities, visceral enlargement, and structural skeletal changes occur at some point during the course of the illness in most patients. Progressive neurologic deterioration develops in a minority.^{3,4}

Enzyme replacement was proposed as a therapeutic strategy for Gaucher's disease in 1966.⁵ It was demonstrated in 1974 that single intravenous infusions of purified placental glucocerebrosidase markedly reduced hepatic and blood glucocerebrosidase levels.⁶ Extension of these initial studies required the development of a large-scale procedure for purifying the

enzyme.⁷ However, trials of replacement therapy with the enzyme prepared according to the new method gave inconsistent results,⁸ presumably because most of the enzyme injected was taken up by hepatocytes.⁹ Since glucocerebrosidase does not accumulate in hepatocytes in patients with Gaucher's disease,¹⁰ it was necessary to target the exogenous enzyme to macrophages, in which the lipid is stored. Several targeting strategies¹¹⁻¹³ that took advantage of the mannose lectin on the macrophage plasma membrane¹⁴ were examined. Of these, sequential deglycosylation of the oligosaccharide chains of the native enzyme was the most effective and permitted efficient delivery of glucocerebrosidase to the lysosomes of macrophages.^{15,16} Objective clinical responses were observed in a child with type 1 Gaucher's disease treated with this substance in a pilot study.¹⁷ We report here the clinical effectiveness of macrophage-targeted human placental glucocerebrosidase as a therapeutic agent in 12 patients with nonneuronopathic Gaucher's disease.

METHODS

Patients

Twelve patients with nonneuronopathic type 1 Gaucher's disease were selected for participation in the trial from among patients referred to the Developmental and Metabolic Neurology Branch of the National Institute of Neurological Disorders and Stroke. The diagnosis was confirmed by assaying glucocerebrosidase activity in extracts of cultured skin fibroblasts. Patients were required to be at least six years old and to have an intact spleen; they could be of either sex. The hemoglobin level at the time of entry into the study had to be less than 110 g per liter. All participants were serologically nonreactive for hepatitis B surface antigen and human immunodeficiency virus (HIV) and had no evidence of intercurrent cardiopulmonary, renal, infectious, or neoplastic disease. A complete series of vaccinations against poliovirus was required of all participants, as was a negative pregnancy test of all female patients of childbearing age.

Approval of the protocol was granted by the institutional review board before the study began. Written informed consent was ob-

From the Developmental and Metabolic Neurology Branch (N.W.B., R.O.B., G.J.M., C.E.A., R.P.G., K.-T.Y.) and the Biometry and Field Studies Branch (J.M.D.), National Institute of Neurological Disorders and Stroke; the Liver Diseases Section, National Institute of Diabetes and Digestive and Kidney Diseases (A.M.D.); the Departments of Diagnostic Radiology (S.C.H.) and Clinical Pathology (R.I.P.), Clinical Center; all at the National Institutes of Health, Bethesda, Md.; and the Department of Orthopedic Surgery (S.H.D., H.J.M.), Massachusetts General Hospital, Boston. Address reprint requests to Dr. Barton at Bldg. 10, Rm. 3D04, National Institutes of Health, Bethesda, MD 20892.

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The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher's disease: a systematic review

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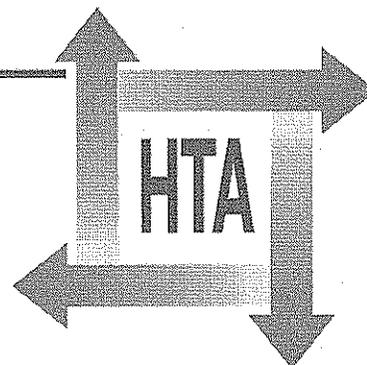
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Executive summary

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Executive summary

Objective

Enzyme replacement therapy (ERT; intravenous imiglucerase) is used in the treatment of people with symptomatic type I and type III Gaucher's disease in order to reduce symptoms of the disease and prevent long-term damage. The aim of this review is to determine the clinical effectiveness and cost-effectiveness of ERT in the treatment of symptomatic Gaucher's disease.

Background

Gaucher's disease

Gaucher's disease is an inherited disorder caused by deficient activity of the enzyme glucocerebrosidase, found mainly in lysosomes. This results in an accumulation of glucocerebroside in the lysosomes of macrophages, predominantly in the reticuloendothelial system. Consequences of this abnormal storage include:

- visceral problems: hepatomegaly, splenomegaly, anaemia and thrombocytopenia causing fatigue, discomfort, infections, bleeding and bruising
- bone problems: pain (acute or chronic) and bone crises, and avascular necrosis
- other problems such as lung disease, impaired growth and delayed puberty.

The severity of symptoms and rate of progression vary considerably from patient to patient and range from asymptomatic to severe with early death. The variability is partly related to genotype (over 200 different mutations have been identified). Although, at a population level, different genotypes tend to be associated with certain phenotypes, making it difficult to generalise findings from one country to another, the relationship between genotype and phenotype is not rigid, as background genetics and environment also play a role. Prediction of the clinical course of an individual patient based on genotype alone is uncertain.

Gaucher's disease is classified into three subtypes by clinical features. Type I can present at any age and has predominantly visceral symptoms without neurological effects. Type II causes severe

progressive brain disease and death occurs in infancy. Type III presents in childhood and has neurological and visceral symptoms.

Imiglucerase (Cerezyme[®]) is a recombinant enzyme modified to enhance its uptake into lysosomes. It is given intravenously to replace the defective enzyme and is licensed for use in symptomatic type I disease and to treat the visceral symptoms of type III disease. Intravenous Cerezyme[®] cannot cross the blood-brain barrier and is not effective for neurological manifestations.

Prevalence

Over 90% of affected individuals have type I Gaucher's disease. It is rare, affecting between 1 in 40,000 and 1 in 60,000 individuals. There are thought to be around 250 people affected in England and Wales. Type III is even rarer, affecting less than 1 in 100,000 individuals. The focus of this report is mainly type I Gaucher's disease.

The NHS

This technology is already widely used in the NHS as patients with significant clinical symptoms have had access to the therapy following the recommendations of the National Specialist Commissioning Advisory Group. Current provision of ERT is said to cost the NHS in England and Wales around £20 million per annum. Although this currently represents a steady state, if ERT reduces disease-specific mortality, the figure will grow as the population being treated ages. Extending use to patients who are mildly symptomatic or asymptomatic individuals as a prophylactic measure would also increase the burden on the NHS.

Methods

Given the paucity of evidence from randomised controlled trials (RCTs) and controlled studies that compare ERT with alternative treatments, it was decided a priori to seek information from all study designs, including uncontrolled or poorly controlled studies, and from patient registries. The aim was to review and synthesise this information to estimate the likely clinical effectiveness and cost-effectiveness of ERT.

Original Article

The effect of enzyme replacement therapy on bone crisis and bone pain in patients with type 1 Gaucher disease

Charrow J, Dulisse B, Grabowski GA, Weinreb NJ. The effect of enzyme replacement therapy on bone crisis and bone pain in patients with type 1 Gaucher disease.

Clin Genet 2007: 71: 205–211. © Blackwell Munksgaard, 2007

The effect of enzyme replacement therapy (ERT) on bone crisis and bone pain was investigated in patients with Gaucher disease (GD) type 1 followed over 4 years. Data from the International Collaborative Gaucher Group Gaucher Registry were used. Only patients with bone crisis and/or bone pain data for 1 year prior to ERT, and for each of 3 years after the start of ERT, were included. Bone crises were reported in 17% of patients during the year before starting ERT. The frequencies of bone crises decreased to 5%, <1% and 3% for 1, 2, and 3 years after initiation of treatment, respectively ($p < 0.0001$). Bone pain followed a similar pattern of response. Bone pain was reported in 49% of patients the year before treatment and decreased to 30% in the first year, 29% in the second year, and 30% in the third year of ERT ($p < 0.0001$). ERT is associated with a reduction in bone crisis and bone pain in patients with GD type 1. This study shows that significant improvements in symptoms of skeletal disease are achievable clinical outcomes and treatment goals in GD type 1.

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Key words: bone crisis – bone pain – enzyme replacement therapy – Gaucher disease – imiglucerase

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Gaucher disease (GD) is the most common lysosomal disorder. It results from deficient activity of acid β -glucosidase (EC 3.2.1.45; glucocerebrosidase), which leads to the accumulation of glucosylceramide in organs that contain large numbers of cells in the monocytic/macrophage lineage (1). GD type 1 is differentiated from GD type 2 and GD type 3 by the absence of primary central nervous system involvement (1).

The bone marrow and mineralized skeleton are prominent sites of pathology in GD type 1 (1, 2). Nearly all patients have radiologic evidence of bone marrow infiltration and expansion because of the presence of populations of characteristic macrophage-derived storage Gaucher cells (1–3).

Untreated, many patients suffer progressive and often disabling morbidity attributable to skeletal complications, including osteopenia, lytic lesions, pathological fractures, avascular necrosis, and joint destruction (3–5). Skeletal manifestations can be severe in both splenectomized patients and those with intact spleens. Affected patients can have major skeletal disease in the presence of asymptomatic hepatosplenomegaly and/or minimally altered hematologic parameters (3, 5–6).

Symptoms of bone disease in patients with GD include bone crisis and bone pain (1, 3). Bone crises are often associated with acute bone infarction. They typically begin with regional dull, aching pains that become intense and

Review of miglustat for clinical management in Gaucher disease type I

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Abstract: Gaucher disease is a progressive lysosomal storage disorder caused by the deficiency of glucocerebrosidase, and characterized by intralysosomal storage of glucosylceramide that leads to dysfunction in multiple organ systems. Intravenous enzyme replacement with imiglucerase is the accepted standard for treatment of symptomatic patients and has been effective in reducing many of the signs and symptoms of type I Gaucher disease in the majority of patients without serious adverse effects. An alternative therapeutic approach is substrate reduction therapy with N-butyldeoxynojirimycin (NB-DNJ) (miglustat; Zavesca®), an imino sugar that reversibly inhibits glucosylceramide synthase and reduces intracellular storage of glucosylceramide. Miglustat was recently approved in Europe and the United States for symptomatic patients with mild to moderate clinical manifestations for whom enzyme replacement therapy is not an option. This review article discusses the results of clinical studies and use of miglustat as a therapeutic agent in patients with type I Gaucher disease.

Keywords: Gaucher disease, miglustat, substrate reduction therapy

First described by Dr. Philippe Gaucher in 1882, Gaucher disease is a lysosomal storage disorder that is caused by the deficiency of glucocerebrosidase, and is characterized by the accumulation of glycosylceramide that leads to dysfunction in multiple organ systems (Beutler and Grabowski 1995). Three types of Gaucher disease have been described, but, actually, these represent different degrees of severity along a spectrum. The clinical features of type I Gaucher disease, the non-neuronopathic form, are splenomegaly, which is more prominent than the hepatomegaly, anemia, thrombocytopenia, and bone lesions. Type II Gaucher disease is the most severe form, which presents with severe central nervous system involvement and is generally fatal within the first 2 years of life. Type III Gaucher disease, the subacute neuronopathic form, presents in early childhood with severe manifestations resembling type I (splenomegaly, hepatomegaly, and bone lesions) and has a more chronic course with onset of neurological disease towards the end of the first decade (Beutler and Grabowski 1995).

In 1991, the advent of targeted enzyme replacement therapy (ERT) using alglucerase (Ceredase®; Genzyme Corporation) followed by the introduction of imiglucerase (Cerezyme®; Genzyme Corporation) resulted in huge improvements in the treatment of patients with Gaucher disease. Imiglucerase is a modified form of glucocerebrosidase, created using recombinant DNA technology, and is given as intravenous infusions, usually every other week. Imiglucerase acts like the naturally occurring enzyme glucocerebrosidase to break down the glucosylceramide that has accumulated in Gaucher cells (Barton et al 1991; Grabowski et al 1998). In the majority of patients (>90%), ERT has been effective in reducing many of the signs and symptoms of type I Gaucher disease but has no or limited effect on the neurologic findings of type II and III Gaucher disease because of its inability to cross the blood – brain barrier (Weinreb et al 2002).

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Quality of life assessment in adults with type 1 Gaucher disease

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Abstract. The effect of enzyme replacement therapy on health-related quality of life in 25 adults with type 1 Gaucher disease was investigated over a 2-year period. Quality of life was assessed using the SF-36 Health Survey (SF-36). Psychological functioning was assessed using the Symptom Checklist-90R. The results indicated significant improvement in 7 of 8 SF scale scores beginning at 18 months of therapy ($P < 0.05$ to 0.001). The SF scale showing improvement first was Vitality (energy level and fatigue) at 6 months of therapy ($P < 0.01$). The SF-36 scales showing the largest improvements were Role-Physical and Social Functioning ($P < 0.001$). Compared to

the general US adult population, the study population's health profile was significantly lower prior to starting therapy but by 24 months of therapy there were no differences between the two. No differences were found in psychological functioning compared to a US adult normative group at the start of therapy. However, within the study population there was significant improvement in mood and global functioning and fewer psychological symptoms reported at 24 months of therapy. The findings indicate that enzyme replacement therapy for type 1 Gaucher disease has a positive impact on health-related quality of life from the patient's perspective.

Key words: Enzyme replacement therapy, Gaucher disease, Quality of life

Introduction

Gaucher disease is an autosomal recessive genetic disorder in which there is deficiency of the lysosomal enzyme glucocerebrosidase and accumulation of glycosphingolipids. Lipid deposit occurs primarily in the spleen, liver and bone marrow with resultant organ dysfunction and clinical symptomatology [1]. Chronic, non-neuronopathic Gaucher type 1 is the most prevalent form of the disorder. Incidence is estimated to be 1/40,000–60,000 in the non-Ashkenazi Jewish population and up to 1/1000 in the Ashkenazi Jewish group. Patients with type 1 disease show significant variability in age of clinical presentation, in severity of symptoms and in long-term disability. Patients may be asymptomatic or manifest some combination of anemia, thrombocytopenia, hepatosplenomegaly and/or bone disease [2].

Gene identification has allowed for delineation of five mutations which account for the vast majority of molecular defects in the Ashkenazi Jewish population (95%) and somewhat less (50%) for the non-Jewish cases [3]. Although there has been some general correlation between specific mutation burden and severity of clinical symptoms, correlation is not

invariant and clinical course is largely unpredictable [4]. This is particularly true of bone disease which may be insidious in onset and progression but eventually disabling [5].

The development of enzyme replacement therapy in 1990 ushered in a new era of treatment for Gaucher disease. Effectiveness of treatment as monitored by physiologic parameters has been documented for many but not all patients [6, 7]. Because enzyme replacement therapy is costly and must be maintained for life, assessment of general health improvement, both physical and mental, is critical to evaluating the value of therapeutic intervention. This is particularly important given the phenotypic variability in the clinical course of patients, both with and without enzyme replacement. Given the extraordinary cost and the degree of uncertainty in predicting the clinical course of the disease, understanding the potential benefits of therapy beyond improvements in physiological parameters and observable symptoms is relevant [4, 8, 9].

Measurement of health-related quality of life is now widely used in health outcomes research and longitudinal monitoring of health status [10–12]. The current study was conducted to assess type 1 Gaucher

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Gaucher Disease

Synonyms: Glucocerebrosidase Deficiency, Glucosylceramidase Deficiency. Includes: Gaucher Disease Type 1; Gaucher Disease Type 2 (Acute); Gaucher Disease Type 3 (Subacute/Chronic); Gaucher Disease, Perinatal-Lethal Form; Gaucher Disease, Cardiovascular Form

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Summary

Disease characteristics. Gaucher disease (GD) encompasses a continuum of clinical findings from a perinatal lethal disorder to an asymptomatic type. The identification of three major clinical types (1, 2, and 3) and two other subtypes (perinatal-lethal and cardiovascular) is useful in determining prognosis and management. GD type 1 is characterized by the presence of clinical or radiographic evidence of bone disease (osteopenia, focal lytic or sclerotic lesions, and osteonecrosis), hepatosplenomegaly, anemia and thrombocytopenia, lung disease, and the absence of primary central nervous system disease. GD types 2 and 3 are characterized by the presence of primary neurologic disease; in the past, they were distinguished by age of onset and rate of disease progression, but these distinctions are not absolute. Disease with onset before age two years, limited psychomotor development, and a rapidly progressive course with death by age two to four years is classified as GD type 2. Individuals with GD type 3 may have onset before age two years, but often have a more slowly progressive course and may live into the third or fourth decade. The perinatal-lethal form is associated with ichthyosiform or collodion skin abnormalities or with nonimmune hydrops fetalis. The cardiovascular form is characterized by calcification of the aortic and mitral valves, mild splenomegaly, corneal opacities, and supranuclear ophthalmoplegia. Cardiopulmonary complications have been described with all the clinical subtypes, although varying in frequency and severity.

Diagnosis/testing. The diagnosis of GD relies on demonstration of deficient glucosylceramidase enzyme activity in peripheral blood leukocytes or other nucleated cells. Carrier testing by assay of enzyme activity is unreliable because of overlap in enzyme activity between carriers and non-carriers. Identification of two disease-causing alleles in *GBA*, the only gene in which mutations are known to cause GD, provides additional confirmation of the diagnosis but should not be used for diagnosis in lieu of biochemical testing.

Management. *Treatment of manifestations:* When possible, management by a multidisciplinary team at a Comprehensive Gaucher Center. For persons not receiving enzyme replacement therapy (ERT) or substrate reduction therapy (SRT), symptomatic treatment includes partial or total splenectomy for massive splenomegaly and thrombocytopenia. Supportive care for all affected individuals may include: transfusion of blood products for severe anemia and bleeding, analgesics for bone pain, joint replacement surgery for relief from chronic pain and restoration of function, and oral bisphosphonates and calcium for osteopenia.

Prevention of primary manifestations: ERT is usually well tolerated and provides sufficient exogenous enzyme to overcome the block in the catabolic pathway, clearing the stored substrate, GL1, and thus reversing hematologic and liver/spleen involvement. Individuals with severe GD, primarily those with chronic neurologic involvement (GD type 3), can benefit from bone marrow transplantation (BMT). Miglustat may be indicated in symptomatic individuals with GD type 1 who are not able to receive ERT.

Original Article

Improvement of bone disease by imiglucerase (Cerezyme) therapy in patients with skeletal manifestations of type 1 Gaucher disease: results of a 48-month longitudinal cohort study

OnlineOpen: This article is available free online at www.blackwell-synergy.com

Sims KB, Pastores GM, Weinreb NJ, Barranger J, Rosenbloom BE, Packman S, Kaplan P, Mankin H, Xavier R, Angell J, Fitzpatrick MA, Rosenthal D. Improvement of bone disease by imiglucerase (Cerezyme) therapy in patients with skeletal manifestations of type 1 Gaucher disease: results of a 48-month longitudinal cohort study. Clin Genet 2008; 73: 430–440. © Blackwell Munksgaard, 2008

Progressive skeletal disease accounts for some of the most debilitating complications of type 1 Gaucher disease. In this 48-month, prospective, non-randomized, open-label study of the effect of enzyme replacement therapy on bone response, 33 imiglucerase-naïve patients (median age 43 years with one or more skeletal manifestations such as osteopenia, history of bone crisis, or other documented bone pathology) received imiglucerase 60 U/kg/2 weeks. Substantial improvements were observed in bone pain (BP), bone crises (BC), and bone mineral density (BMD). Improvements in BP were observed at 3 months ($p < 0.001$ vs baseline) and continued progressively throughout the study, with 39% of patients reporting pain at 48 months vs 73% at baseline. Eleven of the 13 patients with a pre-treatment history of BC had no recurrences. Biochemical markers for bone formation increased; markers for bone resorption decreased. Steady improvement of spine and femoral neck BMD, measured using dual-energy X-ray absorptiometry was noted. Mean Z score for spine increased from -0.72 ± 1.302 at baseline to near-normal levels (-0.09 ± 1.503) by month 48 ($p = 0.042$) and for femoral neck from -0.59 ± 1.352 to -0.17 ± 1.206 ($p = 0.035$) at month 36. This increase was sustained at 48 months. With imiglucerase treatment, patients should anticipate resolution of BC, rapid improvement in BP, increases in BMD, and decreased skeletal complications.

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Key words: bone disease – Gaucher disease – imiglucerase – skeletal manifestations

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Effectiveness of Enzyme Replacement Therapy in 1028 Patients with Type 1 Gaucher Disease after 2 to 5 Years of Treatment: A Report from the Gaucher Registry

Neal J. Weinreb, MD, Joel Charrow, MD, Hans C. Andersson, MD, Paige Kaplan, MD, Edwin H. Kolodny, MD, Pramod Mistry, MD, Gregory Pastores, MD, Barry E. Rosenbloom, MD, C. Ronald Scott, MD, Rebecca S. Wappner, MD, Ari Zimran, MD

PURPOSE: Gaucher disease is the first lysosomal storage disorder to be treated with macrophage-targeted enzyme replacement therapy. Previous studies in relatively small numbers of patients demonstrated short-term efficacy of this treatment. This study describes the effects of 2 to 5 years of treatment on specific manifestations of type 1 Gaucher disease.

SUBJECTS AND METHODS: Physicians reported data from 1028 patients to the Gaucher Registry. Assessment of response included serial measurements of hemoglobin concentration, platelet count, liver and spleen volumes, and the occurrence of bone pain and bone crises.

RESULTS: Among anemic patients, hemoglobin concentration increased to normal or near normal within 6 to 12 months, with a sustained response through 5 years. In thrombocytopenic patients with intact spleens, the most rapid response oc-

curred during the first 2 years, with slower improvement thereafter. The likelihood of achieving a normal platelet count decreased with increasing severity of baseline thrombocytopenia. In patients who had undergone splenectomy, platelet counts returned to normal within 6 to 12 months. Hepatomegaly decreased by 30% to 40% during follow-up; splenomegaly decreased 50% to 60%, but rarely to volumes below five times normal size. In patients with pretreatment bone pain or bone crises, 52% (67/128) were pain free after 2 years and 94% (48/51) reported no additional crises.

CONCLUSION: Enzyme replacement therapy prevents progressive manifestations of Gaucher disease, and ameliorates Gaucher disease-associated anemia, thrombocytopenia, organomegaly, bone pain, and bone crises. *Am J Med.* 2002;113:112-119. ©2002 by Excerpta Medica, Inc.

Type 1 Gaucher disease is a multi-system disease caused by a genetic deficiency of lysosomal glucocerebrosidase (1). Its clinical manifestations include anemia, thrombocytopenia, hepatosplenomegaly, and bone dysplasia (2). Treatment with macrophage-tar-

geted enzyme replacement therapy (alglucerase, derived from human placental tissue, or imiglucerase, a recombinant enzyme with the same clinical effectiveness as alglucerase [3]) ameliorates anemia and thrombocytopenia, decreases organomegaly (4), and may improve or prevent the progression of bone disease (5).

The individual response to treatment is difficult to predict because the clinical expression of disease is highly variable. This report from the Gaucher Registry presents the 2- to 5-year effects of enzyme replacement therapy on the specific manifestations of the disease as a benchmark for assessment of individual responses in terms of hematologic abnormalities, organomegaly, skeletal pain, and bone crises.

METHODS

Patients

The organization of the Gaucher Registry has been described by Charrow et al. (6). Eligible patients had type 1 Gaucher disease and were treated with alglucerase (Ceredase, Genzyme Corporation, Cambridge, Massachusetts) or imiglucerase (Cerezyme, Genzyme Corporation) for at least 6 months. All patients had baseline (pretreatment) data and at least one response parameter during 6 to 60 months of monitoring. Treatment dosage and frequency

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This study was supported in part by a grant from Genzyme Corporation, Cambridge, Massachusetts. The Gaucher Registry is sponsored by Genzyme Corporation.

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Effect of Enzyme Replacement Therapy With Imiglucerase on BMD in Type 1 Gaucher Disease

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ABSTRACT: The effect of ERT with imiglucerase on BMD in type 1 GD was studied using BMD data from the International Collaborative Gaucher Group Gaucher Registry. Data were analyzed for 160 untreated patients and 342 ERT-treated patients. Imiglucerase significantly improves BMD in patients with GD, with 8 years of ERT leading to normal BMD.

Introduction: The objective was to determine the effect of enzyme replacement therapy (ERT; Cerezyme, imiglucerase) on BMD in type 1 Gaucher disease (GD).

Materials and Methods: The study population included all adults (men, 18–70 years; women, 18–50 years) enrolled in the International Collaborative Gaucher Group (ICGG) Gaucher Registry for whom lumbar spine BMD measurements were available. BMD data with up to 8 years of follow-up were analyzed for 160 patients who received no ERT and 342 patients treated with ERT alone. BMD was assessed by DXA of the lumbar spine. Z scores for patients with GD were compared with a reference population. From the model's estimate, percent of patients by age and sex with osteoporosis (T score ≤ -2.5) were calculated.

Results: DXA Z scores for patients with GD in the no ERT (untreated) group were significantly below normal (y intercept = -0.80 Z score units, $p < 0.001$) and remained ~ 1 SD below the reference population over time (slope = -0.010 Z score units per year, $p = 0.68$). The DXA Z scores for patients with GD who received ERT at a dose of 60 U/kg/2 weeks were significantly lower than the reference population at baseline (y-intercept = -1.17 Z score units, $p < 0.001$), but improved significantly over time (slope = $+0.132$ Z score units per year, $p < 0.001$). A significant dose–response relationship was noted for the ERT group, with the slopes for the three main dosing groups of 15, 30, and 60 U/kg/2 weeks of $+0.064$, $+0.086$, and $+0.132$ Z score units per year, respectively. The BMD of patients with GD treated with ERT increased to -0.12 (60 U/kg/2 weeks), -0.48 (30 U/kg/2 weeks), and -0.66 (15 U/kg/2 weeks) SD of the mean of the reference population after 8 years of ERT, approaching the reference population. Estimated risk of osteoporosis of this GD population, if left untreated, ranged from ~ 10 to 30% in women and 10% to 25% in men.

Conclusions: ERT with imiglucerase (Cerezyme) may increase BMD in patients with GD. Response to treatment with imiglucerase is slower for BMD than for hematologic and visceral aspects of GD. A normal (age- and sex-adjusted) BMD should be a therapeutic goal for patients with type 1 GD.

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Key words: type 1 Gaucher disease, enzyme replacement therapy, BMD, DXA, bone densitometry

INTRODUCTION

GAUCHER DISEASE (GD) is a progressive, multisystemic and debilitating disorder that is caused by a deficiency of the lysosomal enzyme, glucocerebrosidase, which leads

to the pathologic accumulation of the enzyme substrate, glucocerebroside, within the tissue macrophages of multiple organs.⁽¹⁾ Type 1 GD (non-neuronopathic) is the most prevalent form (94%) and is differentiated from type 2 (acute neuronopathic, 1%) and type 3 (chronic neuronopathic, 5%) by the absence of central nervous system involvement.⁽²⁾ The clinical manifestations of type 1 GD include splenomegaly, hepatomegaly, anemia, thrombocytopenia, and bone disease. The bone manifestations of GD are multifaceted and can include bone marrow infiltration,

Dr Kacena is the Principal Statistician for and owns stock in Genzyme Corp. Dr Zimran is a member of the ICGG registry program supported by Genzyme Corp. Drs Pastores and Kaplan receive research grants from Genzyme Corp. All other authors state that they have no conflicts of interest.

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Phase 1/2 and extension study of velaglucerase alfa replacement therapy in adults with type 1 Gaucher disease: 48-month experience

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Phase 1/2 and extension study of velaglucerase alfa replacement therapy in adults with type 1 Gaucher disease: 48-month experience

Ari Zimran,¹ Gheona Altarescu,¹ Mici Philips,¹ Drorit Attias,¹ Marina Jmoudiak,¹ Maher Deeb,¹ Nan Wang,² Kiran Bhirangi,² Gabriel M. Cohn,² and Deborah Elstein¹

¹Gaucher Clinic, Shaare Zedek Medical Center, Jerusalem, Israel; and ²Shire Human Genetic Therapies Inc, Cambridge, MA

Enzyme replacement therapy is the standard of care for symptomatic Gaucher disease. Velaglucerase alfa is a human β -glucocerebrosidase produced in a well-characterized human cell line. A 9-month phase 1/2 open-label, single-center trial and ongoing extension study were conducted to evaluate safety and efficacy of velaglucerase alfa. Twelve symptomatic adult type 1 Gaucher patients (intact spleens) received velaglucerase alfa (60 U/kg per infusion) during phase 1/2. An extension study was offered to pa-

tients completing the trial; step-wise dose reduction (to 30 U/kg per infusion) was instituted. Eleven patients completed phase 1/2; 10 entered the extension; 9 patients reached 39 months of extension. No drug-related serious adverse events or withdrawals, and no antibodies were observed. Home therapy was successfully implemented during the extension. Statistically significant improvements ($P < .004$) were noted in mean percentage change from baseline to 9 months and baseline to 48 months for hemoglobin

(+19.2%, +21.7%, respectively), platelet counts (+67.6%, +157.8%, respectively), normalized liver volume (-18.2%, -42.8%, respectively), and normalized spleen volume (-49.5%, -79.3%, respectively). These significant clinical changes and safety profile led to phase 3 trials and highlight the potential of velaglucerase alfa as alternative therapy for type 1 Gaucher disease. The extension trial is registered at <http://www.clinicaltrials.gov> as NCT00391625. (*Blood*. 2010;115(23):4651-4656)

Introduction

Gaucher disease (GD) is a multisystem disorder involving the liver, spleen, bone marrow, skeleton, lungs, and occasionally the central nervous system. GD is an autosomal recessive, lysosomal storage disease caused by the deficiency of β -glucocerebrosidase.¹ Enzyme replacement therapy (ERT) is currently the standard of care for the treatment of symptomatic Gaucher disease. Alglucerase injection (Ceredase; Genzyme Corporation), a mannose-terminated placental-derived β -glucocerebrosidase was the first enzyme formulation approved by the Food and Drug Administration (FDA) for the treatment of type 1 GD. Imiglucerase for injection (Cerezyme; Genzyme Corporation), a recombinant analog of β -glucocerebrosidase produced in Chinese hamster ovary cells, received FDA approval in 1994 and gradually replaced alglucerase. Both enzymatic preparations have been generally well tolerated and efficacious in the improvement of type 1 Gaucher-related hematologic abnormalities and reduction of hepatosplenomegaly.¹⁻³

Velaglucerase alfa (formerly known as gene-activated human glucocerebrosidase [GA-GCB]) is an investigational human β -glucocerebrosidase, produced in a human cell line using proprietary Gene Activation technology (Shire Human Genetic Therapies Inc [Shire HGT]). It is a monomeric glycoprotein (~63 kDa, containing 5 potential N-linked glycosylation sites) that targets macrophages via mannose receptors, and acts to degrade accumulated glucocerebroside within the macrophages.⁴ The amino acid sequence of velaglucerase alfa is identical to that of the human, wild-type enzyme, unlike imiglucerase, which differs from the wild-type human enzyme sequence by a single amino acid substitution at position 495.² Another distinguishing structural feature is that velaglucerase alfa has higher α -mannosyl content than imiglucerase.

To evaluate the safety and efficacy of velaglucerase alfa, a phase 1/2 trial was performed. The primary objective was to assess the safety of velaglucerase alfa administered intravenously at a dose of 60 U/kg every other week for 9 months in adult patients with symptomatic type 1 (nonneuronopathic) Gaucher disease (GD1). The secondary objective of this trial was to assess the clinical activity of velaglucerase alfa on key disease features.¹ The extension study was similarly designed to evaluate the long-term safety and assess the effects of velaglucerase alfa on 4 disease measures: hemoglobin concentration, platelet count, liver volume, and spleen volume.¹ The results of the 9-month phase 1/2 open-label, single-center study of velaglucerase alfa and its 39-month extension, through 48 total months, are reported here.

Methods

The phase 1/2 and extension study were conducted in a single center (Gaucher Clinic, Shaare Zedek Medical Center). These studies were conducted in compliance with US Food and Drug Administration regulations and approved by the Gaucher Clinic Institutional Helsinki (Ethics) Committee and the Israeli Ministry of Health. The start of the phase 1/2 trial (April 2004) predated the July 2005 requirement for registration with National Institutes of Health. The extension trial was registered as NCT00391625 (<http://www.clinicaltrials.gov/ct/show/NCT00391625?order=8>).

Patients

Adult, symptomatic, enzymatically confirmed patients with GD1 were screened. Eligibility criteria included age of 18 years or older, an intact

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imiglucerase for injection

200 UNITS

400 UNITS

DESCRIPTION

Cerezyme[®] (imiglucerase for injection) is an analogue of the human enzyme β -glucocerebrosidase, produced by recombinant DNA technology. β -Glucocerebrosidase (β -D-glucosyl-N-acylsphingosine glucosylhydrolase, E.C. 3.2.1.45) is a lysosomal glycoprotein enzyme which catalyzes the hydrolysis of the glycolipid glucocerebroside to glucose and ceramide.

Cerezyme[®] is produced by recombinant DNA technology using mammalian cell culture (Chinese hamster ovary). Purified imiglucerase is a monomeric glycoprotein of 497 amino acids, containing 4 N-linked glycosylation sites (Mr = 60,430). Imiglucerase differs from placental glucocerebrosidase by one amino acid at position 495, where histidine is substituted for arginine. The oligosaccharide chains at the glycosylation sites have been modified to terminate in mannose sugars. The modified carbohydrate structures on imiglucerase are somewhat different from those on placental glucocerebrosidase. These mannose-terminated oligosaccharide chains of imiglucerase are specifically recognized by endocytic carbohydrate receptors on macrophages, the cells that accumulate lipid in Gaucher disease.

Cerezyme[®] is supplied as a sterile, non-pyrogenic, white to off-white lyophilized product. The quantitative composition of the lyophilized drug is provided in the following table:

Ingredient	200 Unit Vial	400 Unit Vial
Imiglucerase (total amount)*	212 units	424 units
Mannitol	170 mg	340 mg
Sodium Citrates (Trisodium Citrate) (Disodium Hydrogen Citrate)	70 mg (52 mg) (18 mg)	140 mg (104 mg) (36 mg)
Polysorbate 80, NF	0.53 mg	1.06 mg
Citric Acid and/or Sodium Hydroxide may have been added at the time of manufacture to adjust pH.		

*This provides a respective withdrawal dose of 200 and 400 units of imiglucerase.

An enzyme unit (U) is defined as the amount of enzyme that catalyzes the hydrolysis of 1 micromole of the synthetic substrate para-nitrophenyl- β -D-glucopyranoside (pNP-Glc) per minute at 37°C. The product is stored at 2-8°C (36-46°F). After reconstitution with Sterile Water for Injection, USP, the imiglucerase concentration is 40 U/mL (see **DOSAGE AND ADMINISTRATION** for final concentrations and volumes). Reconstituted solutions have a pH of approximately 6.1.

CLINICAL PHARMACOLOGY

Mechanism of Action/Pharmacodynamics

Gaucher disease is characterized by a deficiency of β -glucocerebrosidase activity, resulting in accumulation of glucocerebroside in tissue macrophages which become engorged and are typically found in the liver, spleen, and bone marrow and occasionally in lung, kidney, and intestine. Secondary hematologic sequelae include severe anemia and thrombocytopenia in addition to the characteristic progressive hepatosplenomegaly, skeletal complications, including osteonecrosis and osteopenia with secondary pathological fractures. **Cerezyme**[®] (imiglucerase for injection) catalyzes the hydrolysis of glucocerebroside to glucose and ceramide. In clinical trials, **Cerezyme** improved anemia and thrombocytopenia, reduced spleen and liver size, and decreased cachexia to a degree similar to that observed with Ceredase[®] (alglucerase injection).

Pharmacokinetics

During one-hour intravenous infusions of four doses (7.5, 15, 30, 60 U/kg) of **Cerezyme**[®] (imiglucerase for injection), steady-state enzymatic activity was achieved by 30 minutes. Following infusion, plasma enzymatic activity declined rapidly with a half-life ranging from 3.6 to 10.4 minutes. Plasma clearance ranged from 9.8 to 20.3 mL/min/kg (mean \pm S.D., 14.5 \pm 4.0 mL/min/kg). The volume of distribution corrected for weight ranged from 0.09 to 0.15 L/kg (0.12 \pm 0.02 L/kg). These variables do not appear to be influenced by dose or duration of infusion. However, only one or two patients were studied at each dose level and infusion rate. The pharmacokinetics of **Cerezyme** do not appear to be different from placental-derived alglucerase (Ceredase[®]).

In patients who developed IgG antibody to **Cerezyme**, an apparent effect on serum enzyme levels resulted in diminished volume of distribution and clearance and increased elimination half-life compared to patients without antibody (see **WARNINGS**).

INDICATIONS AND USAGE

Cerezyme[®] (imiglucerase for injection) is indicated for long-term enzyme replacement therapy for pediatric and adult patients with a confirmed diagnosis of Type 1 Gaucher disease that results in one or more of the following conditions:

- anemia
- thrombocytopenia
- bone disease
- hepatomegaly or splenomegaly

CONTRAINDICATIONS

There are no known contraindications to the use of **Cerezyme**[®] (imiglucerase for injection). Treatment with **Cerezyme** should be carefully re-evaluated if there is significant clinical evidence of hypersensitivity to the product.

WARNINGS

Approximately 15% of patients treated and tested to date have developed IgG antibody to **Cerezyme**[®] (imiglucerase for injection) during the first year of therapy. Patients who developed IgG antibody did so largely within 6 months of treatment and rarely developed antibodies to **Cerezyme** after 12 months of therapy. Approximately 46% of patients with detectable IgG antibodies experienced symptoms of hypersensitivity.

Patients with antibody to **Cerezyme** have a higher risk of hypersensitivity reaction. Conversely, not all patients with symptoms of

hypersensitivity have detectable IgG antibody. It is suggested that patients be monitored periodically for IgG antibody formation during the first year of treatment.

Treatment with **Cerezyme** should be approached with caution in patients who have exhibited symptoms of hypersensitivity to the product.

Anaphylactoid reaction has been reported in less than 1% of the patient population. Further treatment with imiglucerase should be conducted with caution. Most patients have successfully continued therapy after a reduction in rate of infusion and pretreatment with antihistamines and/or corticosteroids.

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PRECAUTIONS

General

In less than 1% of the patient population, pulmonary hypertension and pneumonia have also been observed during treatment with **Cerezyme**[®] (imiglucerase for injection). Pulmonary hypertension and pneumonia are known complications of Gaucher disease and have been observed both in patients receiving and not receiving **Cerezyme**. No causal relationship with **Cerezyme** has been established. Patients with respiratory symptoms in the absence of fever should be evaluated for the presence of pulmonary hypertension.

Therapy with **Cerezyme** should be directed by physicians knowledgeable in the management of patients with Gaucher disease.

Caution may be advisable in administration of **Cerezyme** to patients previously treated with Ceredase[®] (alglucerase injection) and who have developed antibody to Ceredase or who have exhibited symptoms of hypersensitivity to Ceredase.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies have not been conducted in either animals or humans to assess the potential effects of **Cerezyme**[®] (imiglucerase for injection) on carcinogenesis, mutagenesis, or impairment of fertility.

Teratogenic Effects: Pregnancy Category C

Animal reproduction studies have not been conducted with **Cerezyme**[®] (imiglucerase for injection). It is also not known whether **Cerezyme** can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. **Cerezyme** should not be administered during pregnancy except when the indication and need are clear and the potential benefit is judged by the physician to substantially justify the risk.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when **Cerezyme**[®] (imiglucerase for injection) is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of **Cerezyme**[®] (imiglucerase for injection) have been established in patients between 2 and 16 years of age. Use of **Cerezyme** in this age group is supported by evidence from adequate and well-controlled studies of **Cerezyme** and Ceredase[®] (alglucerase injection) in adults and pediatric patients, with additional data obtained from the medical literature and from long-term post-marketing experience. **Cerezyme** has been administered to patients younger than 2 years of age, however the safety and effectiveness in patients younger than 2 have not been established.

ADVERSE REACTIONS

Since the approval of **Cerezyme**[®] (imiglucerase for injection) in May 1994, Genzyme has maintained a worldwide post-marketing database of spontaneously reported adverse events and adverse events discussed in the medical literature. The percentage of events for each reported adverse reaction term has been calculated using the number of patients from these sources as the denominator for total patient exposure to **Cerezyme** since 1994. Actual patient exposure is difficult to obtain due to the voluntary nature of the database and the continuous accrual and loss of patients over that span of time. The actual number of patients exposed to **Cerezyme** since 1994 is likely to be greater than estimated from these voluntary sources and, therefore, the percentages calculated for the frequencies of adverse reactions are most likely greater than the actual incidences.

Experience in patients treated with **Cerezyme** has revealed that approximately 13.8% of patients experienced adverse events which were judged to be related to **Cerezyme** administration and which occurred with an increase in frequency. Some of the adverse events were related to the route of administration. These include discomfort, pruritus, burning, swelling or sterile abscess at the site of venipuncture. Each of these events was found to occur in < 1% of the total patient population.

Symptoms suggestive of hypersensitivity have been noted in approximately 6.6% of patients. Onset of such symptoms has occurred during or shortly after infusions; these symptoms include pruritus, flushing, urticaria, angioedema, chest discomfort, dyspnea, coughing, cyanosis, and hypotension. Anaphylactoid reaction has also been reported (see **WARNINGS**). Each of these events was found to occur in < 1.5% of the total patient population. Pre-treatment with antihistamines and/or corticosteroids and reduced rate of infusion have allowed continued use of **Cerezyme** in most patients.

Additional adverse reactions that have been reported in approximately 6.5% of patients treated with **Cerezyme** include: nausea, abdominal pain, vomiting, diarrhea, rash, fatigue, headache, fever, dizziness, chills, backache, and tachycardia. Each of these events was found to occur in < 1.5% of the total patient population.

Incidence rates cannot be calculated from the spontaneously reported adverse events in the post-marketing database. From this database, the most commonly reported adverse events in children (defined as ages 2 – 12 years) included dyspnea, fever, nausea, flushing, vomiting, and coughing, whereas in adolescents (>12 – 16 years) and in adults (>16 years) the most commonly reported events included headache, pruritus, and rash.

In addition to the adverse reactions that have been observed in patients treated with **Cerezyme**, transient peripheral edema has been reported for this therapeutic class of drug.

OVERDOSE

Experience with doses up to 240 U/kg every 2 weeks have been reported. At that dose there have been no reports of obvious toxicity.

DOSAGE AND ADMINISTRATION

Cerezyme[®] (imiglucerase for injection) is administered by intravenous infusion over 1-2 hours. Dosage should be individualized to each patient. Initial dosages range from 2.5 U/kg of body weight 3 times a week to 60 U/kg once every 2 weeks. 60 U/kg every 2 weeks is the dosage for which the most data are available. Disease severity may dictate that treatment be initiated at a relatively high dose or relatively frequent administration.

Dosage adjustments should be made on an individual basis and may increase or decrease, based on achievement of therapeutic goals as assessed by routine comprehensive evaluations of the patient's clinical manifestations.

Cerezyme[®] should be stored at 2-8°C (36-46°F). After reconstitution, **Cerezyme** should be inspected visually before use. Because this is a protein solution, slight flocculation (described as thin translucent fibers) occurs occasionally after dilution. The diluted solution may be filtered through an in-line low protein-binding 0.2 μ m filter during administration. Any vials exhibiting opaque particles or discoloration should not be used. DO NOT USE **Cerezyme** after the expiration date on the vial.

On the day of use, after the correct amount of **Cerezyme** to be administered to the patient has been determined, the appropriate number of vials are each reconstituted with Sterile Water for Injection, USP. The final concentrations and administration volumes are provided in the following table:

	200 Unit Vial	400 Unit Vial
Sterile water for reconstitution	5.1 mL	10.2 mL
Final volume of reconstituted product	5.3 mL	10.6 mL
Concentration after reconstitution	40 U/mL	40 U/mL
Withdrawal volume	5.0 mL	10.0 mL
Units of enzyme within final volume	200 units	400 units

A nominal 5.0 mL for the 200 unit vial (10.0 mL for the 400 unit vial) is withdrawn from each vial. The appropriate amount of **Cerezyme** for each patient is diluted with 0.9% Sodium Chloride Injection, USP, to a final volume of 100 – 200 mL. **Cerezyme** is administered by intravenous infusion over 1-2 hours. Aseptic techniques should be used when diluting the dose. Since **Cerezyme** does not contain any preservative, after reconstitution, vials should be promptly diluted and not stored for subsequent use. **Cerezyme**, after reconstitution, has been shown to be stable for up to 12 hours when stored at room temperature (25°C) and at 2-8°C. **Cerezyme**, when diluted, has been shown to be stable for up to 24 hours when stored at 2-8°C.

Relatively low toxicity, combined with the extended time course of response, allows small dosage adjustments to be made occasionally to avoid discarding partially used bottles. Thus, the dosage administered in individual infusions may be slightly increased or decreased to utilize fully each vial as long as the monthly administered dosage remains substantially unaltered.

HOW SUPPLIED

Cerezyme[®] (imiglucerase for injection) is supplied as a sterile, non-pyrogenic, lyophilized product. It is available as follows:

200 Units per Vial NDC 58468-1983-1
400 Units per Vial NDC 58468-4663-1

Store at 2-8°C (36-46°F).

Rx only

Cerezyme[®] (imiglucerase for injection) is manufactured by:
Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142 USA

Certain manufacturing operations may have been performed by other firms.

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6LE0005D

Genzyme.ERT Diagnostic Code & Billing Table

Product	Manufacturer	HCPCS	Indication	ICD-9-CM
Cerezyme [®] (imiglucerase for injection)	Genzyme	J1786 Injection, imiglucerase, 10 units	Type I Gaucher Disease	272.7 Lipidosis
Fabrazyme [®] (agalsidase beta)	Genzyme	J0180 Injection agalsidase beta, per 1 mg	Fabry Disease	272.7 Lipidosis
Aldurazyme [®] (laronidase)	Genzyme	J1931 Injection laronidase per .1 mg	Mucopolysaccharidosis I	277.5 Mucopolysaccha ridosis
Lumizyme [®] (alglucosidase alfa)	Genzyme	J0221Lumizyme injection per 10 mg	Pompe Disease	271.0 Glycogenosis
Myozyme [®] (alglucosidase alfa)	Genzyme	J0220 Alglucosidase alfa Injection per 10 mg	Pompe Disease	271.0 Glycogenosis
ELELYSO [™] (taliglucerase alfa)	Pfizer	J3490 Unclassified Drug or J3590 Unclassified Biologic	Type I Gaucher Disease	272.7 Lipidosis
Naglazyme [®] (galsulfase)	BioMarin	J1458 Injection, galsulfase, per 1 mg	Maroteaux-Lamy Syndrome Mucopolysaccharidosis VI	277.5 Mucopolysaccha ridosis
ELAPRASE [®] (idursulfase)	Shire	J1743 Idursulfase Injection 1mg	Hunter Syndrome Mucopolysaccharidosis II	277.5 Mucopolysaccha ridosis
VPRIV (velaglucerase alfa)	Shire	J3385 Injection velaglucerase alfa, per 100 units	Type I Gaucher Disease	272.7 Lipidosis

Current Procedural Terminology (CPT) codes used when administering enzyme replacement therapy via intravenous infusion:

- **CPT 96365** Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
- **CPT 96366** Intravenous infusion, for therapy, prophylaxis, or diagnosis; each additional hour

Minimum Recommendations for Monitoring Patients with Non-Neuronopathic (Type 1) Gaucher Disease

Initial Assessment^{1,2}

Blood Tests	
PRIMARY TESTS	ADDITIONAL TESTS AS INDICATED⁵
Hemoglobin	AST and/or ALT Albumin
Platelet Count	Alkaline Phosphatase Total Protein
Biochemical Markers ³	Calcium Serum Immunoelectrophoresis
• Chitotriosidase	Phosphorus Iron
• ACE	PT Iron Binding Capacity
• Acid Phosphatase, tartrate resistant (TRAP)	PTT Ferritin
Mutation Analysis	WBC Vitamin B ₁₂
Antibody Sample ⁴	Total and Direct Bilirubin
Visceral ⁶	
Spleen Volume (Volumetric MRI or CT)	
Liver Volume (Volumetric MRI or CT)	
Skeletal	
MRI (coronal; T1- & T2-weighted) of entire femora ⁷	
X-ray: AP view of entire femora ⁷ and lateral view of spine	
DEXA: lumbar spine and femoral neck	
Bone Age (for patients age 14 years or less) ⁵	
Pulmonary ⁸	
ECG, Chest X-ray, and Doppler Echocardiogram (right ventricular systolic pressure) for patients >18 years old	
Quality of Life	
Patient-reported functional health and well-being (SF-36 Health Survey)	

Ongoing Monitoring²

	Patients Not on Enzyme Therapy	Patients on Enzyme Therapy			
		Not Achieved Therapeutic Goals	Achieved Therapeutic Goals	At Time of Dose Change or Significant Clinical Complication	
	Every 12 Months	Every 12-24 Months	Every 3 Months	Every 12 Months	Every 12-24 Months
Blood Tests					
Hemoglobin	X		X		X
Platelet Count	X		X		X
Biochemical Markers ³	X		X		X
• Chitotriosidase					
• ACE					
• Acid Phosphatase, tartrate resistant (TRAP)					
Visceral ⁶					
Spleen Volume (Volumetric MRI or CT)		X		X	X
Liver Volume (Volumetric MRI or CT)		X		X	X
Skeletal					
MRI (coronal; T1- & T2-weighted) of entire femora ⁷		X		X	X
X-ray: AP view of entire femora ⁷ and lateral view of spine		X		X	X
DEXA: lumbar spine and femoral neck		X		X	X
Quality of Life					
Patient-reported functional health and well-being (SF-36 Health Survey)	X		X	X	X

1. A complete patient and family history, preferably including a pedigree, should be conducted.
2. A comprehensive physical examination should be performed at least annually.
3. One or more of these biochemical markers should be consistently monitored at least every 12 months and in conjunction with other clinical assessments of disease activity and response to treatment.
Of the three recommended markers, chitotriosidase, when available as a validated procedure from an experienced laboratory, may be the most sensitive indicator of changing disease activity, and is therefore preferred.
4. A baseline sample will be drawn and stored at Genzyme. A subsequent sample is suggested to be drawn at 6 months after starting ERT but is optional. The baseline and additional samples will be tested only if clinically indicated, such as for a suspected immune-mediated adverse event, prior to a switch to home therapy, or for suspected loss of ERT effectiveness.
5. These should be followed appropriately if abnormal based on each patient's age and clinical status.
6. Obtain contiguous transaxial 10 mm thick sections for sum of region of interest.
7. Optimally, obtain hips to below knees.
8. Pulmonary assessments are recommended every 12-24 months for patients with borderline or above normal pulmonary pressures at baseline.

International Coordinators of the Gaucher Registry

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Effective Health Care Program

Technical Brief
Number 12

Enzyme-Replacement Therapies for Lysosomal Storage Diseases



Agency for Healthcare Research and Quality
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Enzyme-Replacement Therapies for Lysosomal Storage Diseases

Structured Abstract

Background. Lysosomal storage diseases (LSDs) comprise about 50 unique monogenic autosomal or X-linked diseases with an estimated combined incidence of 1 in 77,000 to 88,000 live births. They occur secondary to genetic mutations that result in deficiency or reduced activity of native intracellular enzymes that catabolize biological macromolecules. These enzyme defects result in accumulation of specific macromolecular compounds within lysosomes in various tissues and organs, causing progressive damage that can become life-threatening in some diseases. LSD management traditionally involved supportive care measures tailored to disease stage, the organs and systems involved, and the degree of impairment. However, enzyme-replacement therapy (ERT) is now commercially available for six LSDs, typically used lifelong with traditional management practices for each.

Purpose. The objective of this Technical Brief is to provide an overview of U.S. Food and Drug Administration (FDA)-approved ERT for the treatment of six LSDs. The purpose of a Technical Brief is to report what outcomes (benefits and harms) have been studied for a technology, drug or procedure; it does not enumerate those outcomes. The Technical Brief also addresses research gaps identified during its preparation. It is not intended as a comparative effectiveness review or systematic review that draws conclusions as to the clinical benefits and harms of a drug, device, or procedure. It does not assess study quality or the strength of the body of evidence on specific outcomes.

Methods. Four Guiding Questions were used to frame this Technical Brief. An inspection of the literature from 1990 through mid-April 2012 included primary studies, as well as narrative and systematic review articles to create an overview of potential clinical outcomes. Other information sources included dosing and other treatment-related information from the FDA-approved product labels; scientific information packages from the product manufacturers that included unpublished data; and, interviews with physician Key Informants and patient advocates.

Findings. Published clinical studies report a variety of outcomes associated with nine FDA-approved ERT products. They include disease-specific intermediate outcomes, such as plasma or urinary levels of macromolecular compounds. Others were common hematological measures (e.g., anemia, thrombocytopenia), bone pain and skeletal abnormalities, renal function, cardiac function, pulmonary function, growth, and walking tests. Harms reported to the FDA and in clinical studies were primarily allergic, including infusion-associated reactions and anaphylaxis. Immunogenic responses, primarily an IgG-type antibody response and neutralizing antibodies, have been reported. This Technical Brief identified a number of research gaps, including the need for comparative effectiveness studies, dose optimization, optimal timing for initiation of ERT, and mechanisms involved in uptake and distribution of ERT products.

Silver Compounds For Dental Caries

Question: Should coverage for silver compounds (silver nitrate plus topical fluoride or silver diamine fluoride) to prevent and treat dental caries be added to the Prioritized List?

Question source: Senator Bates

Issue: At the December 13, 2012 VBBS meeting, the evidence on the use of silver compounds (specifically silver diamine fluoride) was reviewed, and public testimony was heard about the pros and cons of use of silver nitrate plus fluoride varnish for the arresting of dental caries.

Summary of the evidence

Silver diamine fluoride appears to be effective at preventing and arresting caries based on evidence only performed resource-poor settings (and none in the United States). There are no studies on silver nitrate + fluoride which is what would be used in the U.S. There are no studies evaluating the utility of arresting of caries compared to standard of care which is immediate restoration compared to delayed restoration.

Summary of the argument in favor of silver compounds

- It stops the infection in the tooth
- Silver is coming back into favor
- Allows for those who do not want restoration (or immediate restoration) to have a means to arrest caries progression
- Inexpensive chemical
- Anecdotal evidence from Advantage that it is decreasing their ED visits

Summary of the argument against silver compounds

- There is no data in the US supporting this as a treatment
- There are no known studies in process actually evaluating the efficacy of arresting caries compared to immediate restorative treatment
- There is permanent tooth discoloration that occurs
- Restoration is still required
- There is a potential large cost associated with the recommended 5 visits over 3-4 months, and then there would still be the cost of restoration
- No professional associations recommend it

Oregon Board of Dentistry input

From Patrick Braatz, Executive Director, Oregon Board of Dentistry

“No official position it is something that Dentists may use.

The Board has recently developed an administrative rule to allow Dental Hygienists and dental assistants to also apply if a dentist has authorized, but that rule has not yet passed.”

Silver Compounds For Dental Caries

AAPD Clinical Guideline, updated 2011.

Guideline on Caries-risk Assessment and Management for Infants, Children, and Adolescents.

-- one of the advocates stated that AAPD recommended it.

The clinical guideline had the following language:

“ Other approaches to the assessment and treatment of dental caries will emerge with time and, with evidence of effectiveness, may be included in future guidelines on caries risk assessment and management protocols. For example, there are emerging trends to use calcium and phosphate remineralizing solution to reverse dental caries.⁵³ Other fluoride compounds, such as **silver diamine fluoride⁵⁴** and **stannous fluoride⁵⁵**, may be more effective than sodium fluoride for topical applications.”

Conclusion: Silver diamine fluoride may be included in future guidelines as evidence of effectiveness emerges

American Dental Association: Center for Evidence-based Dentistry

- No official position
1. Critical summary January 2011 of the following review: *Rosenblatt A, Stamford TC, Niederman R. Silver diamine fluoride: a caries "silver-fluoride bullet". Journal of Dental Research. 2009;88(2):116-25*
 2. Strengths and Weaknesses of the Systematic Review:
The reviewers used accepted methods to identify and select studies on SDF based on a priori inclusion criteria and the two studies reached similar conclusions. The reported preventive fractions and numbers needed to treat in the systematic review did not compare the SDF to fluoride varnish, and instead compared outcomes for SDF and fluoride varnish to the control groups.
 3. Strengths and Weaknesses of the Evidence:
Both studies in the review were prospective studies with relatively large numbers of subjects in each study group, which was the main strength. While one of the studies compared SDF to no treatment, the other compared SDF to fluoride varnish. In addition, Chu and colleagues (2002) did not estimate trial sample sizes using a priori power calculations. Safety outcome measures associated with SDF were not clearly defined. There are potential problems with concluding that SDF is safe based on results from a study that may not be adequately powered to detect differences in adverse outcomes that are rare. Lastly, one study assessed the effectiveness of SDF on primary maxillary anterior teeth while the other focused on primary canines, primary molars, and permanent first molars.
 4. Implications for Dental Practice:

Silver Compounds For Dental Caries

Results from two studies suggest that SDF is a promising chemotherapeutic agent that arrests and prevents caries in children. However, SDF has not been approved by the FDA for clinical use in the United States. Additional studies are needed to assess safety. There are also concerns associated with staining caused by SDF, which can be addressed by restoring the SDF-treated teeth with glass ionomer. SDF may have the potential to be used in clinical settings as a chemotherapeutic agent to effectively control and reduce dental caries in high-risk populations.

Summary

There is evidence in resource-poor countries that silver diamine fluoride is effective at preventing and arresting caries. However, there is no evidence of the effectiveness of silver nitrate + fluoride varnish which is what would be used in the US (because the FDA has not approved silver diamine fluoride) and there are no US studies of either type of treatment. There are concerns about costs of repeated visits when restoration is still required and there is no data supporting that delayed restoration compared to immediate restoration is beneficial. Cosmetic concerns about permanent black staining in the teeth exist. Although the international studies are promising, no US major dental organizations currently recommend the use of silver compounds. This appears to be an experimental treatment at this time, and more research demonstrating efficacy and safety is required prior to allowing OHP patients to have this procedure done.

Recommendations:

- 1) Do not add silver treatments to the Prioritized List
- 2) Add a guideline to indicate that neither this treatment (Silver diamine fluoride) nor a proxy (silver nitrate plus fluoride) are included on the Prioritized List

Guideline Note XX Silver compounds for dental caries

Lines 58, 372, 373, 494, 621

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

Guideline on Caries-risk Assessment and Management for Infants, Children, and Adolescents

Originating Council

Council on Clinical Affairs

Review Council

Council on Clinical Affairs

Adopted

2002

Revised

2006, 2010, 2011

Purpose

The American Academy of Pediatric Dentistry (AAPD) recognizes that caries-risk assessment and management protocols can assist clinicians with decisions regarding treatment based upon caries risk and patient compliance and are essential elements of contemporary clinical care for infants, children, and adolescents. This guideline is intended to educate healthcare providers and other interested parties on the assessment of caries risk in contemporary pediatric dentistry and aid in clinical decision making regarding diagnostic, fluoride, dietary, and restorative protocols.

Methods

This guideline is an update of AAPD's "Policy on Use of a Caries-risk Assessment Tool (CAT) for Infants, Children, and Adolescents, Revised 2006" that includes the additional concepts of dental caries management protocols. The update used electronic and hand searches of English written articles in the medical and dental literature within the last 10 years using the search terms "caries risk assessment", "caries management", and "caries clinical protocols". From this search, 1,909 articles were evaluated by title or by abstract. Information from 75 articles was used to update this document. When data did not appear sufficient or were inconclusive, recommendations were based upon expert and/or consensus opinion by experienced researchers and clinicians.

Background

Caries-risk assessment

Risk assessment procedures used in medical practice normally have sufficient data to accurately quantitate a person's disease susceptibility and allow for preventive measures.¹ Even though caries-risk data in dentistry still are not sufficient to quantitate the models, the process of determining risk should be a component in the clinical decision making process.² Risk assessment:

1. fosters the treatment of the disease process instead of treating the outcome of the disease;

2. gives an understanding of the disease factors for a specific patient and aids in individualizing preventive discussions;
3. individualizes, selects, and determines frequency of preventive and restorative treatment for a patient; and
4. anticipates caries progression or stabilization.

Caries-risk assessment models currently involve a combination of factors including diet, fluoride exposure, a susceptible host, and microflora that interplay with a variety of social, cultural, and behavioral factors.³⁻⁶ Caries risk assessment is the determination of the likelihood of the incidence of caries (ie, the number of new cavitated or incipient lesions) during a certain time period⁷ or the likelihood that there will be a change in the size or activity of lesions already present. With the ability to detect caries in its earliest stages (ie, white spot lesions), health care providers can help prevent cavitation.⁸⁻¹⁰

Caries risk indicators are variables that are thought to cause the disease directly (eg, microflora) or have been shown useful in predicting it (eg, socioeconomic status) and include those variables that may be considered protective factors. Currently, there are no caries-risk factors or combinations of factors that have achieved high levels of both positive and negative predictive values.² Although the best tool to predict future caries is past caries experience, it is not particularly useful in young children due to the importance of determining caries risk before the disease is manifest. Children with white spot lesions should be considered at high risk for caries since these are precavitated lesions that are indicative of caries activity.¹¹ Plaque accumulation also is strongly associated with caries development in young children.^{12,13} As a corollary to the presence of plaque,¹⁴ a child's mutans streptococci levels³ and the age at which a child becomes colonized with cariogenic flora^{15,16} are valuable in assessing risk, especially in preschool children.

While there is no question that fermentable carbohydrates are a necessary link in the causal chain for dental caries, a systematic study of sugar consumption and caries risk has concluded that the relationship between sugar consumption and caries is much weaker in the modern age of fluoride exposure

From American Dental Association: Center for Evidence-based Dentistry

<http://ebd.ada.org/SystematicReviewSummaryPage.aspx?srlId=340901e6-21b5-43b4-abd1-c749c720e057>

Limited evidence suggests that silver diamine fluoride may effectively arrest and prevent dental caries in children

Critical Summary Prepared by: Donald L. Chi D.D.S., PhD

OVERVIEW

Systematic Review Conclusion:

Silver diamine fluoride (SDF) is more effective than, and as safe as, fluoride varnish in arresting and preventing dental caries.

Critical Summary Assessment:

The results of two studies, only one of which was a nonrandomized study that directly compared silver diamine fluoride and fluoride varnish, suggest that silver fluoride diamine fluoride is more effective at arresting and preventing caries on primary maxillary anterior teeth.

Evidence Quality Rating: Limited

A Critical Summary of:

Silver diamine fluoride: a caries "silver-fluoride bullet"

Rosenblatt A, Stamford TC, Niederman R. Journal of Dental Research. 2009;88(2):116-25

Clinical Questions:

Compared to fluoride varnish, is silver diamine fluoride a) more effective at arresting and preventing caries? and b) safer?

Review Methods:

The authors searched five databases (MEDLINE, LILACS, EMBASE, Cochrane Library, Brazilian Dental Library) for studies that met the following criteria: 1) assessed silver diamine fluoride as a caries-preventive therapy in humans; 2) published between 1966 and 2006; 3) published in English, Spanish, or Portuguese; 4) adopted a randomized controlled trial, cohort trial, or case-control design; 5) analyzed patients as the unit of observation; and 5) reported variance estimates. Two investigators conducted the review and a third investigator resolved disagreements. Data from the studies were used to calculate

two outcomes: prevented fraction (caries arrest or prevention in the treatment group compared to the control group) and the numbers needed to treat (number of children who would need to be treated to prevent one additional decayed tooth surface).

Main Results:

The authors identified 110 unique studies, from which 12 relevant studies were selected for further review. After reviewing the bibliographies of these 12 studies, three additional studies were selected for review. Two of the 15 studies met all the inclusion criteria. The first was a 30-month prospective cohort trial (N=308) that compared SDF to fluoride varnish. The second was a 36-month prospective cohort trial (N=373) that compared SDF to no treatment. Data from the two studies were not aggregated to generate pooled outcome measures. The reported prevented fractions for arresting active caries ranged from 55.6 percent to 122 percent for SDF and 14.2 percent to 21.3 percent for fluoride varnish. The reported prevented fractions for preventing new caries ranged from 63.6 percent to 83.5 percent (SDF) and 43.7 percent to 55.7 percent (fluoride varnish). For both outcome measures, compared to controls (either water or no treatment), the reported numbers needed to treat were 0.6 to 10 (SDF) and 1.1 to 5.6 (fluoride varnish). Neither study reported significant differences in adverse outcomes between the treatment and control groups.

Conclusion:

Silver diamine fluoride is more effective than fluoride varnish at arresting active caries and preventing new caries. SDF is equally as safe as fluoride varnish.

Source of funding:

Fulbright Program and The Forsyth Institute.

Commentary:

Importance and Context:

Although chemotherapeutic agents such as fluoride varnish are known to inhibit dental caries by decreasing acid solubility, high caries rates persist in certain population subgroups (Brickhouse et al. 2008; Parker et al. 2010). High caries rates have stimulated efforts to identify chemotherapeutic agents that will control the infection. To date, a systematic review has not been conducted to assess the effectiveness and safety of SDF.

Strengths and Weaknesses of the Systematic Review:

The reviewers used accepted methods to identify and select studies on SDF based on a priori inclusion criteria and the two studies reached similar conclusions. The reported preventive fractions and numbers needed to treat in the systematic review did not compare the SDF to fluoride varnish, and instead compared outcomes for SDF and fluoride varnish to the control groups.

Strengths and Weaknesses of the Evidence:

Both studies in the review were prospective studies with relatively large numbers of subjects in each study group, which was the main strength. While one of the studies compared SDF to no treatment, the other compared SDF to fluoride varnish. In addition, Chu and colleagues (2002) did not estimate trial sample sizes using a priori power calculations. Safety outcome measures associated with SDF were not clearly defined. There are potential problems with concluding that SDF is safe based on results from a study that may not be adequately powered to detect differences in adverse outcomes that are rare. Lastly, one study assessed the effectiveness of SDF on primary maxillary anterior teeth while the other focused on primary canines, primary molars, and permanent first molars.

Implications for Dental Practice:

Results from two studies suggest that SDF is a promising chemotherapeutic agent that arrests and prevents caries in children. However, SDF has not been approved by the FDA for clinical use in the United States. Additional studies are needed to assess safety. There are also concerns associated with staining caused by SDF, which can be addressed by restoring the SDF-treated teeth with glass ionomer. SDF may have the potential to be used in clinical settings as a chemotherapeutic agent to effectively control and reduce dental caries in high-risk populations.

REFERENCES

Brickhouse TH, Rozier RG, Slade GD. Effects of enrollment in medicaid versus the state children's health insurance program on kindergarten children's untreated dental caries. *Am J Public Health*. 2008 May;98(5):876-81. Epub 2008 Apr 1

Parker EJ, Jamieson LM, Broughton J, Albino J, Lawrence HP, Roberts-Thomson K. The oral health of Indigenous children: a review of four nations. *J Paediatr Child Health*. 2010 Sep;46(9):483-6. doi: 10.1111/j.1440-1754.2010.01847.x.

Section 6

Coverage Guidance Review

CG – Viscosupplementation for the Knee

Question: How should the HERC approved Coverage Guidance – Viscosupplementation for the knee—be incorporated into the Prioritized List?

Question source: Health Evidence Review Commission

Issue: HERC approved the Coverage Guidance: Viscosupplementation for the knee in October, 2012. This coverage guidance needs to be evaluated for application within the Prioritized List.

HERC Coverage Guidance

Viscosupplementation should not be covered for the treatment of pain associated with Osteoarthritis (OA) of the knee.

Current Prioritized List status:

CPT 20610 (Arthrocentesis, aspiration, and/or injection; major joint or bursa (e.g. shoulder, hip, knee joint) is used to for viscosupplementation of the knee. This CPT code is found on lines 52, 84, 151, 161, 308, 384, 406, 443, 455, 489, 529, 531, 549, 619, 623, and 634. Osteoarthritis of the knee (715.16, .26, .36, .96) is found on lines 384 RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, OSTEOCHONDRITIS DISSECANS, AND ASEPTIC NECROSIS OF BONE and 489 OSTEOARTHRITIS AND ALLIED DISORDERS. Internal derangement of the knee (ICD-9 716) is located on lines 455 INTERNAL DERANGEMENT OF KNEE AND LIGAMENOUS DISRUPTIONS OF THE KNEE, POTENTIALLY RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT and 638 SPRAINS AND STRAINS OF ADJACENT MUSCLES AND JOINTS, MINOR.

Recommendations:

1. Add the following Guideline to lines 384, 455, and 489.

GUILDELINE XXX, VISCOSUPPLEMENTATION OF THE KNEE

Lines 384, 455, 489

Viscosupplementation of the knee (CPT 20610) is not covered for treatment of osteoarthritis of the knee.

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: VISCOSUPPLEMENTATION FOR OSTEOARTHRITIS OF THE KNEE

DATE: 10/11/2012

HERC COVERAGE GUIDANCE

Viscosupplementation should not be covered for the treatment of pain associated with Osteoarthritis (OA) of the knee.

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. In addition to an evidence-based guideline developed by the Evidence-based Guideline Subcommittee and a health technology assessment developed by the Health Technology Assessment Subcommittee, coverage guidance may utilize an existing evidence report produced in the last 5 years by the Agency for Healthcare Research and Quality, the Medicaid Evidence-based Decisions Project or the Washington Health Technology Assessment Program.

EVIDENCE SOURCES

Hayes, Inc. (2010). *Hyaluronic Acid/Viscosupplementation*. Produced for the Medicaid Evidence-based Decisions Project and the Washington Health Technology Assessment Program. Portland, OR: Center for Evidence-based Policy, Oregon Health and Science University. Retrieved September 10, 2012, from http://www.hta.hca.wa.gov/documents/ha_final_report_042610.pdf

Hayes, Inc. (2010). *Viscosupplementation for osteoarthritis of the knee*. Produced for the Medicaid Evidence-based Decisions Project. Portland, OR: Center for Evidence-based Policy, Oregon Health and Science University. Retrieved September 10, 2012, from <http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/med/index.cfm>

Samson, D. J., Grant, M. D., Ratko, T. A., Bonnell, C. J., Ziegler, K. M., & Aronson, N. (2007). *Treatment of primary and secondary osteoarthritis of the knee*. AHRQ Evidence Report/Technology Assessment No. 157. AHRQ Publication No. 107-E012. Evidence Report/Technology Assessment, (157), 1-157. Retrieved September 10, 2012, from <http://www.ncbi.nlm.nih.gov/books/NBK38385/>

The summary of evidence in this document is derived directly from these evidence sources, and portions are extracted verbatim.

SUMMARY OF EVIDENCE

Clinical Background

Osteoarthritis (OA) is the most common form of chronic articular disease, affecting approximately 27 million adults in the United States. The most commonly affected joint is the knee, with prevalence estimates ranging from 12% to 16%. To date, there is no known cure for OA nor is there a disease-modifying agent. Optimal management generally requires a combination of both nonpharmacological and pharmacological therapies, and joint replacement surgery or a joint salvage procedure may be considered for selected patients with severe symptomatic OA who have not obtained adequate pain relief and functional improvement from medical therapy. Pharmacological therapy generally begins with acetaminophen, followed by nonsteroidal anti-inflammatory drugs (NSAIDs) if sufficient pain relief is not obtained. There is a small risk of systemic adverse effects with NSAIDs. Aspiration of fluid followed by intraarticular injection of a corticosteroid ameliorates pain in some patients, but duration of relief is usually limited to one to three weeks. Additionally, repeated intraarticular injections of corticosteroids have the potential to cause postinjection flare, infection, and progressive, long-term cartilage damage.

Recently, viscosupplementation with hyaluronan has been introduced as an alternative intraarticular injection therapy for OA. Hyaluronans are also known as sodium hyaluronate or hyaluronic acid (HA). Hyaluronic acid is a normal component of synovial fluid and cartilage. The viscous nature of the compound allows it to act as a joint lubricant, whereas its elasticity allows it to act as a shock absorber. Hyaluronic products are characterized by their molecular weight, which varies according to the source of the compound and method of preparation. Five HA products are currently marketed in the United States: Euflexxa[®] (Ferring), Hyalgan[®] (Sanofi-Aventis), Orthovisc[®] (Anika

Therapeutics), Supartz[®] (Seikagaku Corporation), and Synvisc[®] (Genzyme). Synvisc is a derivative of HA that consists of cross-linked polymers; the compound is referred to as Hylan G-F 20. Hyaluronate preparations have been approved by the Food and Drug Administration (FDA) for treatment of pain associated with OA of the knee in patients who have not had an adequate response to nonpharmacological, conservative treatment and simple analgesics. Recent systematic reviews have come to contradictory conclusions regarding the effectiveness of viscosupplementation, and national guidelines vary in their recommendations.

Evidence Review

There is consistent evidence demonstrating that viscosupplementation results in lower mean pain scores and improves mean function scores a few weeks after treatment. However, the magnitude of benefit may be too small to be clinically important. This evidence is derived from a quantitative synthesis of six meta-analyses performed by the Agency for Healthcare Research and Quality in 2007 which included 42 randomized placebo controlled trials and over 5000 patients (Samson 2007). The authors found that the average change in pain score, although consistent and statistically significant, was small, with weighted mean differences in the range of 1.0 to 22.5 on a 100 point visual acuity scale. While there is no definitive definition of clinical significance, several authors, including Sampson, consider a 20 to 40 point improvement on 100 point pain scales to be clinically significant. The authors also reviewed the five previously published study-level meta-analyses that came to a variety of conclusions regarding the efficacy of viscosupplementation. These ranged from negative to moderately positive to strongly positive. The authors of the Samson review considered only one meta-analysis to have reported data and analysis that fully supported the meta-analysis authors' conclusion. This was also the metaanalysis with a negative conclusion—that the *clinical* effectiveness of viscosupplementation has not been proven and that viscosupplementation may be associated with a higher risk of adverse events.

There is a much greater volume of evidence regarding impact on pain than on function, and many studies did not follow patients beyond three months. Therefore, the impact of viscosupplementation on eventual recovery of function is uncertain. Compared with intraarticular corticosteroid injection, viscosupplementation appears to confer longer-lasting benefit, but the evidence was considered low quality. For comparisons with other treatments, there was insufficient evidence to allow any conclusion. Adverse events occur at a frequency of approximately 2% in single courses of treatment and are primarily transient local reactions, although rare, serious reactions are possible. The rate of adverse events per patient has been shown to increase with repeat courses of treatment, but the only available data were for hylan (high-molecular weight HA).

Evidence pertaining to issues other than efficacy and safety is of low quality:

- Available evidence suggests that viscosupplementation may be as effective as NSAIDs (four RCTs) and results in fewer systemic adverse events (two RCTs); in comparison with intraarticular corticosteroids, it has a delayed onset and longer lasting benefit (nine RCTs plus meta-analysis).
- Hylan may have a superior benefit compared with that of non–cross-linked HA, but the magnitude of difference is very uncertain and hylan poses a small increase in the risk of adverse events.
- To date, there is no evidence of a difference in benefit between low and medium molecular weight HA.
- Younger age may be associated with greater efficacy; evidence pertaining to effectiveness by other patient characteristics and history is lacking.

Overall Summary

While the evidence demonstrates that viscosupplementation results in lower mean pain scores and improved mean function scores a few weeks after treatment, the magnitude of benefit may be too small to be clinically important.

PROCEDURE

Viscosupplementation

DIAGNOSES

Osteoarthritis of the knee

APPLICABLE CODES

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
715	Osteoarthrosis and allied disorders Note: Localized, in the subcategories below, includes bilateral involvement of the same site. Includes: arthritis or polyarthritis: degenerative hypertrophic degenerative joint disease osteoarthritis
715.16	Osteoarthrosis localized primary involving lower leg
715.26	Osteoarthrosis localized secondary involving lower leg

CODES	DESCRIPTION
715.36	Osteoarthritis localized not specified whether primary or secondary involving lower leg
715.96	Osteoarthritis unspecified whether generalized or localized involving lower leg
717	Internal derangement of knee Includes: degeneration of articular cartilage or meniscus of knee; rupture, old of articular cartilage or meniscus of knee; tear, old of articular cartilage or meniscus of knee
ICD-9 Volume 3 (procedure codes)	
81.92	Injection of therapeutic substance into joint or ligament as an ICD-9 procedure
ICD-10 Diagnosis Codes	
M15	Polyarthrosis Includes: arthrosis with mention of more than one site Excludes: bilateral involvement of single joint (M16-M19)
M15.0	Primary generalized (osteo)arthrosis
M15.3	Secondary multiple arthrosis
M15.4	Erosive (osteo)arthrosis
M15.8	Other polyarthrosis
M15.9	Polyarthrosis, unspecified
M17	Gonarthrosis (arthrosis of knee)
M17.0	Primary gonarthrosis, bilateral
M17.1	Other primary gonarthrosis
M17.2	Post-traumatic gonarthrosis, bilateral
M17.3	Other post-traumatic gonarthrosis
M17.4	Other secondary gonarthrosis, bilateral
M17.5	Other secondary gonarthrosis
M17.9	Gonarthrosis, unspecified
M19	Other arthrosis
CPT Codes applicable to viscosupplementation	
20610	Arthrocentesis, aspiration, and/or injection; major joint or bursa (e.g. shoulder, hip, knee joint)
CPT Codes applicable to total knee replacement (TKR)	
27440	Arthroplasty, knee tibial plateau
27441	Arthroplasty, knee tibial plateau; with debridement and partial synovectomy
27442	Arthroplasty, femoral condyles, or tibial plateau(s) knee
27443	Arthroplasty, femoral condyles, or tibial plateau(s) knee; with debridement and partial synovectomy
27445	Arthroplasty, knee, hinge prosthesis (e.g., Walldius type)
27446	Arthroplasty, knee condyle and plateau; medial or lateral compartment
27437	Arthroplasty, patella; without prosthesis
27438	Arthroplasty, patella; with prosthesis
27447	Arthroplasty, knee condyle and plateau; medial and lateral compartments with or without patella resurfacing (total knee arthroplasty)
HCPCS Level II Codes for viscosupplementation	
J7321	Hyaluronan or derivative, Hyalgan or Supartz, for intra-articular injection, per dose

CODES	DESCRIPTION
J7323	Hyaluronan or derivative, Euflexxa, for intraarticular injection, per dose
J7324	Hyaluronan or derivative, Orthovisc, for intraarticular injection
J7325	Hyaluronan or derivative, Synvisc or Synvisc-One, for intraarticular injection, 1 mg
HCPCS Level II Codes for intraarticular cortisone injection	
J0702	Injection betamethasone acetate 3 mg and betamethasone sodium phosphate, 3 mg
J0704	Injection, betamethasone sodium phosphate per 4 mg
J1020	Injection, methylprednisone acetate, 20 mg
J1030	Injection, methylprednisone acetate, 40 mg
J1040	Injection, methylprednisone acetate, 80 mg
J1094	Injection, dexamethasone acetate, 1 mg
J1100	Injection, dexamethasone sodium phosphate, 1 mg
J1700	Injection, hydrocortisone acetate, up to 25 mg
J1710	Injection, hydrocortisone sodium phosphate, up to 50 mg
J1720	Injection, hydrocortisone sodium succinate, up to 100 mg
J2650	Injection, prednisolone acetate, up to 1 mL
J2920	Injection methylprednisone sodium succinate up to 40 mg
J2930	Injection methylprednisone sodium succinate up to 125 mg
J3302	Injection triamcinolone diacetate, per 5 mg
J3303	Injection triamcinolone hexacetonide, per 5 mg

Note: Inclusion on this list does not guarantee coverage

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.

CG – Percutaneous Interventions for Low Back Pain

Question: How should the HERC approved Coverage Guidance – Percutaneous interventions for low back pain—be incorporated into the Prioritized List?

Question source: Health Evidence Review Commission

Issue: HERC approved the Coverage Guidance: Percutaneous interventions for low back pain in October, 2012. This coverage guidance needs to be evaluated for application within the Prioritized List.

HERC Coverage Guidance

For radicular low back pain, Epidural steroid injections should be covered for patients with persistent radiculopathy due to herniated lumbar disc; it is recommended that shared decision-making regarding epidural steroid injection include a specific discussion about inconsistent evidence showing moderate short-term benefits, and lack of long-term benefits. If an epidural steroid injection does not offer benefit, repeated injections should not be covered.

Epidural steroid injections should NOT be covered for spinal stenosis.

For radicular low back pain, the following treatments should NOT be covered:

- coblation nucleoplasty
- radiofrequency denervation

For nonradicular low back pain, the following treatments should NOT be covered:

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

CG – Percutaneous Interventions for Low Back Pain

Current Prioritized List status:

CPT code	Code description	Current List/Line(s)	Recommended Changes
20552-20553	Injection, single or multiple trigger point(s)	529,531,619,623	
20600	Arthrocentesis, aspiration and /or injection; small joint or bursa (eg, fingers, toes)	52,84,161,308,443,489,529,531,619,623,634	Remove 720.1 (Spinal enthesopathy) from line 52
20605	intermediate joint or bursa (eg, temporomandibular, acromioclavicular, wrist, elbow or ankle, olecranon bursa)	52,84,161,308,326,443,489,531,561,619,623,634	Remove 720.1 from line 52
20610	major joint or bursa (eg, shoulder, hip, knee joint, subacromial bursa)	52,84,151,161,308,384,406,443,455,489,529,531,549,619,623,634	Remove 720.1 from line 52
22521-22522	Percutaneous vertebroplasty (bone biopsy included when performed), 1 vertebral body, unilateral or bilateral injection; lumbar	Excluded	
22526 - 22527	Percutaneous intradiscal electrothermal annuloplasty, unilateral or bilateral including fluoroscopic guidance; single level	Excluded	
27096	Injection procedure for sacroiliac joint, anesthetic steroid, with image guidance (fluoroscopy or CT) including arthrography when performed	Diagnostic	Excluded
62292	Injection procedure, arterial, for occlusion of arteriovenous malformation, spinal	Excluded	
62310	Injection(s), of diagnostic or therapeutic substance(s) (including anesthetic, antispasmodic, opioid, steroid, other solution), not including neurolytic substances, epidural or subarachnoid; cervical or thoracic	Ancillary	
62311	lumbar , sacral (caudal)	Ancillary	Add to line 400
64412	Injection, anesthetic agent; spinal accessory nerve	Ancillary	
64479	Injection(s), anesthetic agent and/or steroid, transforaminal epidural, with imaging guidance (fluoroscopy or CT); cervical or thoracic, single level	Excluded	
64480	each additional level	Excluded	
64483	Injection(s), anesthetic agent	164 HERPES	Remove from line 164

CG – Percutaneous Interventions for Low Back Pain

	and/or steroid, transforaminal epidural, with imaging guidance (fluoroscopy or CT); lumbar or sacral, single level	ZOSTER; HERPES SIMPLEX AND WITH NEUROLOGICAL AND OPHTHALMOLOGICAL COMPLICATIONS	Add to line 400
64484	each additional level	164	Remove from line 164 Add to line 400
64490-64495	Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint)	Excluded	
64633-64636	Destruction by neurolytic agent, paravertebral facet joint nerve(s), with imaging guidance (fluoroscopy or CT)	Excluded	
96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular	Ancillary	

Diagnosis codes (ICD-9) included in the HERC guidance are found on lines:
 52 RHEUMATOID ARTHRITIS AND OTHER INFLAMMATORY POLYARTHROPATHIES
 400 DISORDERS OF SPINE WITH NEUROLOGIC IMPAIRMENT
 434 SPINAL DEFORMITY, CLINICALLY SIGNIFICANT
 562 ACUTE AND CHRONIC DISORDERS OF SPINE WITHOUT NEUROLOGIC IMPAIRMENT
 607 SPINAL DEFORMITY, NOT CLINICALLY SIGNIFICANT
 638 SPRAINS AND STRAINS OF ADJACENT MUSCLES AND JOINTS, MINOR

Recommendations:

- 1) Move 720.1 (Spinal enthesopathy) [M46.0 in ICD-10] from line 52 RHEUMATOID ARTHRITIS AND OTHER INFLAMMATORY POLYARTHROPATHIES to lines 516 PERIPHERAL ENTHESOPATHIES --MEDICAL THERAPY and 531 PERIPHERAL ENTHESOPATHIES--SURGICAL THERAPY
 - a. Consistent with other enthesopathies
 - b. Will no longer pair with treatment codes for radicular low back pain
- 2) Add lumbar epidural steroid injections (CPT 62311, 64483, 64484) to line 400 DISORDERS OF SPINE WITH NEUROLOGIC IMPAIRMENT with the guideline below
 - a. Rationale: Line 400 contains radicular back pain diagnoses and disk displacement diagnoses

GUIDELINE NOTE XXX, EPIDURAL STEROID INJECTIONS, OTHER PERCUTANEOUS INTERVENTIONS FOR LOW BACK PAIN

Lines 52, 400, 434, 562, 607, 638

Epidural steroid injections (CPT 62311, 64483, 64484) are covered for patients with persistent radiculopathy due to a herniated lumbar disc; it is recommended that shared decision-making regarding epidural steroid

CG – Percutaneous Interventions for Low Back Pain

injection include a specific discussion about inconsistent evidence showing moderate short-term benefits, and lack of long-term benefits. If an epidural steroid injection does not offer benefit, repeated injections should not be covered. Epidural steroid injections are not covered for spinal stenosis or for patients with low back pain without radiculopathy.

The following interventions are not covered for low back pain, with or without radiculopathy: facet joint corticosteroid injection, prolotherapy, intradiscal corticosteroid injection, local injections, botulinum toxin injection, intradiscal electrothermal therapy, therapeutic medial branch block, radiofrequency denervation, sacroiliac joint steroid injection, coblation nucleoplasty, percutaneous intradiscal radiofrequency thermocoagulation, and radiofrequency denervation.

HEALTH EVIDENCE REVIEW COMMISSION (HERC)
COVERAGE GUIDANCE: PERCUTANEOUS INTERVENTIONS
FOR LOW BACK PAIN

DATE: 10/11/2012

[HERC COVERAGE GUIDANCE](#)

For radicular low back pain, Epidural steroid injections should be covered for patients with persistent radiculopathy due to herniated lumbar disc; it is recommended that shared decision-making regarding epidural steroid injection include a specific discussion about inconsistent evidence showing moderate short-term benefits, and lack of long-term benefits. If an epidural steroid injection does not offer benefit, repeated injections should not be covered.

Epidural steroid injections should NOT be covered for central spinal canal stenosis.

For radicular low back pain, the following treatments should NOT be covered:

- coblation nucleoplasty
- radiofrequency denervation

For nonradicular low back pain, the following treatments should NOT be covered:

- facet joint corticosteroid injection
- prolotherapy
- intradiscal corticosteroid injection
- local injections (including trigger point injections)
- botulinum toxin injection
- epidural steroid injection
- intradiscal electrothermal therapy (IDET)
- medial branch block
- radiofrequency denervation
- sacroiliac joint steroid injection
- coblation nucleoplasty
- percutaneous intradiscal radiofrequency thermocoagulation

*Coverage guidance for non-pharmacologic interventions, pharmacologic interventions, and imaging for low back pain are addressed in separate documents.

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 SOURCES

Livingston, C., Little, A., King, V., Pettinari, C., Thielke, A., Pensa, M., Vandegriff, S., & Gordon, C. (2012). *State of Oregon Evidence-based Clinical Guidelines Project. Percutaneous interventions for low back pain: A clinical practice guideline based on the 2009 American Pain Society Guideline (Interventional Therapies, Surgery, and Interdisciplinary Rehabilitation for Low Back Pain)*. Salem: Office for Oregon Health Policy and Research. Retrieved from <http://www.oregon.gov/OHA/OHPR/HERC/Evidence-Based-Guidelines.shtml>

Chou, R., Loesser, J.D., Owens, D.K., Rosenquist, R.W., Atlas, S.J., Baisden, J., et al. (2009). Interventional therapies, surgery, and interdisciplinary rehabilitation for low back pain: An evidence-based clinical practice guideline from the American Pain Society. *Spine*, 34(10), 1066-1077. – *Accompanied by:*

Chou, R., Atlas, S.J., Stanos, S.P., & Rosenquist, R.W. (2009). Nonsurgical interventional therapies for low back pain: A review of the evidence for an American Pain Society clinical practice guideline. *Spine*, 34(10), 1078-1094.

The summary of evidence in this document is derived directly from these evidence sources, and portions are extracted verbatim.

SUMMARY OF EVIDENCE

Clinical Background

Low back pain is the fifth most common reason for all physician visits in the United States. Approximately one quarter of US adults reported having low back pain lasting at least one whole day in the past three months, and 7.6% reported at least one episode of severe acute low back pain within a 1-year period. Low back pain is also very costly. Total incremental direct health care costs attributable to low back pain in the US were estimated at \$26.3 billion in 1998. In addition, indirect costs related to days lost from work are substantial, with approximately 2% of the US work force compensated for back injuries each year.

Many patients have self-limited episodes of acute low back pain and do not seek medical care. Among those who do seek medical care, pain, disability, and return to work typically improve rapidly in the first month. However, up to one third of patients report persistent back pain of at least moderate intensity one year after an acute episode, and one in five report substantial limitations in activity. Approximately 5% of the people with back pain disability account for 75% of the costs associated with low back pain.

Many options are available for evaluation and management of low back pain. However, there has been little consensus, either within or between specialties, on appropriate clinical evaluation and management of low back pain. Numerous studies show unexplained, large variations in use of diagnostic tests and treatments. Despite wide variations in practice, patients seem to experience broadly similar outcomes, although costs of care can differ substantially among and within specialties.

Evidence Review

Recommendation #1: In patients with persistent radiculopathy due to herniated lumbar disc, it is recommended that clinicians discuss risks and benefits of epidural steroid injection as an option (weak recommendation, moderate-quality evidence). It is recommended that shared decision-making regarding epidural steroid injection include a specific discussion about inconsistent evidence showing moderate short-term benefits, and lack of long-term benefits. There is insufficient evidence to adequately evaluate benefits and harms of epidural steroid injection for spinal stenosis.

For radiculopathy due to herniated lumbar disc, evidence on benefits of epidural steroid injection is mixed. Although some higher-quality trials found epidural steroid injection associated with moderate short-term (through up to 6 weeks) benefits in pain or function, others found no differences *versus* placebo injection. Reasons for the discrepancies between trials is uncertain, but could be related to the type of comparator treatment, as trials that compared an epidural steroid injection to an epidural saline or local anesthetic injection tended to report poorer results than trials that compared an

epidural steroid injection to a soft-tissue (usually interspinous ligament) placebo injection. Regardless of the comparator intervention, there is no convincing evidence that epidural steroids are associated with long-term benefits and most trials found no reduction in rates of subsequent surgery. Although serious complications following epidural steroid injection are rare in clinical trials, there are case reports of paralysis and infections. There is insufficient evidence on clinical outcomes to recommend a specific approach for performing epidural steroid injection, or on use of fluoroscopic guidance. In addition, insufficient evidence exists to recommend how many epidural injections to perform, though one higher-quality trial found that if an initial epidural steroid injection did not result in benefits, additional injections over a 6-week period did not improve outcomes.

Decisions regarding use of epidural steroid injection should be based on a shared decision-making process that includes a discussion of the inconsistent evidence for short-term benefit, lack of long-term benefit, potential risks, and costs. Patient preferences and individual factors should also be considered. For example, epidural steroid injection may be a reasonable option for short-term pain relief in patients who are less optimal surgery candidates due to comorbidities. There is insufficient evidence to guide specific recommendations for timing of epidural steroid injection, though most trials enrolled patients with at least subacute (greater than 4 weeks) symptoms.

Evidence on efficacy of epidural steroid injection for spinal stenosis is sparse and shows no clear benefit, though more trials are needed to clarify effects. Although chymopapain chemonucleolysis is effective for radiculopathy due to herniated lumbar disc, it is less effective than discectomy and is no longer widely available in the United States, in part due to risk of severe allergic reactions. Three trials suggest that intradiscal steroid injection has similar efficacy to chemonucleolysis, although none were placebo controlled.

Recommendation #2: In patients with persistent nonradicular low back pain, facet joint corticosteroid injection, prolotherapy, and intradiscal corticosteroid injection are not recommended (strong recommendation, moderate-quality evidence).

Injections and most interventional therapies for nonradicular low back pain target specific areas of the back that are potential sources of pain, including the muscles and soft tissues (botulinum toxin injection, prolotherapy, and local injections), facet joints (facet joint steroid injection, therapeutic medial branch block, and radiofrequency denervation), degenerated intervertebral discs (intradiscal steroid injection, IDET, and related procedures), and sacroiliac joints (sacroiliac joint injection). There is no convincing evidence from randomized trials that injections and other interventional therapies are effective for nonradicular low back pain. Facet joint steroid injection,

prolotherapy and intradiscal steroid injections are not recommended because randomized trials consistently found them to be no more effective than sham therapies.

Recommendation #3: There is insufficient evidence to adequately evaluate benefits of local injections, botulinum toxin injection, epidural steroid injection, intradiscal electrothermal therapy (IDET), therapeutic medial branch block, radiofrequency denervation, sacroiliac joint steroid injection, coblation nucleoplasty, percutaneous intradiscal radiofrequency thermocoagulation or other medications for nonradicular low back pain.

For local injections¹, there is insufficient evidence to accurately judge benefits because available trials are small, lower-quality, and evaluate heterogeneous populations and interventions. Trials of IDET and radiofrequency denervation reported inconsistent results. There were a small number of higher quality trials, and in the case of radiofrequency denervation, the trials had technical or methodologic shortcomings, making it difficult to reach conclusions about benefits. For other interventional therapies, data are limited to one to two small placebo-controlled randomized trials (botulinum toxin injection, epidural steroid injection for nonradicular low back pain, PIRFT and sacroiliac joint steroid injection), or there are no placebo-controlled randomized trials (therapeutic medial branch block, coblation nucleoplasty....or other medications).

[\[Evidence Source\]](#)

Overall Summary

For radiculopathy due to herniated lumbar disc, evidence on benefits of epidural steroid injection is mixed, with some trials finding moderate short-term benefits and others finding no differences. There is no convincing evidence that epidural steroids are associated with long-term benefits and most trials found no reduction in rates of subsequent surgery. For nonradicular low back pain, there is likewise no convincing evidence that injections and other interventional therapies are effective, while there is consistent evidence that facet joint steroid injection, prolotherapy and intradiscal steroid injections are no more effective than sham therapies.

PROCEDURE

Epidural steroid injection

Botulinum toxin injection

Local injections

Facet joint steroid injection

¹ Defined as placement of a local anesthetic into the muscles or soft tissues of the back via a catheter. One type of local injection is trigger point injection.

Therapeutic medial branch block
 Radiofrequency denervation
 Intradiscal steroid injection
 Intradiscal electrothermal therapy (IDET)
 Sacroiliac joint injection
 Chymopapain chemonucleolysis
 Coblation nucleoplasty
 Percutaneous intradiscal radiofrequency thermocoagulation (PIRFT)

DIAGNOSES

Low back pain

APPLICABLE CODES

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
720.1	Spinal enthesopathy
720.2	Sacroiliitis, not elsewhere classified
721.3	Lumbosacral spondylosis without myelopathy
721.42	Spondylosis with myelopathy, lumbar region
721.5	Kissing spine
721.6	Ankylosing vertebral hyperostosis
721.7	Traumatic spondylopathy
721.8	Other allied disorders of spine
721.9	Spondylosis of unspecified site
722.1	Displacement of thoracic or lumbar intervertebral disc without myelopathy
722.2	Displacement of intervertebral disc, site unspecified, without myelopathy
722.32	Schmorl's nodes, lumbar region
722.39	Schmorl's nodes, other region
722.5	Degeneration of thoracic or lumbar intervertebral disc
722.6	Degeneration of intervertebral disc, site unspecified
722.70	Intervertebral disc disorder with myelopathy, unspecified region
722.72	Intervertebral disc disorder with myelopathy, thoracic region
722.73	Intervertebral disc disorder with myelopathy, lumbar region
722.80	Postlaminectomy syndrome, unspecified region
722.82	Postlaminectomy syndrome, thoracic region
722.83	Postlaminectomy syndrome, lumbar region
722.90	Other and unspecified disc disorder, unspecified region
722.92	Other and unspecified disc disorder, thoracic region
722.93	Other and unspecified disc disorder, lumbar region
724	Other and unspecified disorders of back
724.0	Spinal stenosis other than cervical
724.00	Spinal stenosis, unspecified region
724.01	Spinal stenosis, thoracic region
724.02	Spinal stenosis, lumbar region, without neurogenic claudication
724.03	Spinal stenosis, lumbar region, with neurogenic claudication
724.09	Spinal stenosis, other region
724.1	Pain in thoracic spine

CODES	DESCRIPTION
724.2	Lumbago
724.3	Sciatica
724.4	Thoracic or lumbosacral neuritis or radiculitis, unspecified
724.5	Backache, unspecified
724.6	Disorders of sacrum
724.7	Disorders of coccyx
724.70	Unspecified disorder of coccyx
724.71	Hypermobility of coccyx
724.79	Other disorders of coccyx
724.8	Other symptoms referable to back
724.9	Other unspecified back disorders
730.2	Unspecified osteomyelitis
732.0	Juvenile osteochondrosis of spine
733.0	Osteoporosis
737.2	Lordosis (acquired)
737.30	Scoliosis [and kyphoscoliosis], idiopathic
737.39	Other kyphoscoliosis and scoliosis
737.4	Curvature of spine associated with other conditions
737.8	Other curvatures of spine
737.9	Unspecified curvature of spine
738.4	Acquired spondylolisthesis
738.5	Other acquired deformity of back or spine
739.2	Nonallopathic lesions, thoracic region
739.3	Nonallopathic lesions, lumbar region
739.4	Nonallopathic lesions, sacral region
754.2	Congenital musculoskeletal deformities of spine
756.1	Congenital anomalies of spine
846	Sprains and strains of sacroiliac region
847.1	Sprain of thoracic
847.2	Sprain of lumbar
847.3	Sprain of sacrum
847.4	Sprain of coccyx
847.9	Sprain of unspecified site of back
ICD-9 Volume 3 (procedure codes)	
87.24	Other x-ray of lumbosacral spine
88.38	Other computerized axial tomography
88.93	X-ray, other and unspecified
CPT	
0216T	Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with ultrasound guidance; lumbar or sacral, single level
0217T	second level
0218T	third and any additional level(s)
20552	Injection, single or multiple trigger point(s), 1 or 2 muscle(s)
20553	Injection, single or multiple trigger point(s), 3 or more muscle(s)
20600	Arthrocentesis, aspiration and /or injection; small joint or bursa (eg, fingers, toes)
20605	intermediate joint or bursa (eg, temporomandibular, acromioclavicular, wrist, elbow or ankle, olecranon bursa)
20610	major joint or bursa (eg, shoulder, hip, knee joint, subacromial bursa)
22526	Percutaneous intradiscal electrothermal annuloplasty, unilateral or bilateral including

CODES	DESCRIPTION
	fluoroscopic guidance; single level
22527	1 or more additional levels
27096	Injection procedure for sacroiliac joint, anesthetic steroid, with image guidance (fluoroscopy or CT) including arthrography when performed
62292	Injection procedure, arterial, for occlusion of arteriovenous malformation, spinal
64412	Injection, anesthetic agent; spinal accessory nerve
64483	Injection(s), anesthetic agent and/or steroid, transforaminal epidural, with imaging guidance (fluoroscopy or CT); lumbar or sacral, single level
64484	Injection(s), anesthetic agent and/or steroid, transforaminal epidural, with imaging guidance (fluoroscopy or CT); lumbar or sacral, each additional level
64493	Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with image guidance (fluoroscopy or CT); lumbar or sacral, single level
64494	second level
64495	third and any additional level(s)
64635	Destruction by neurolytic agent, paravertebral facet joint nerve(s), with imaging guidance (fluoroscopy or CT); lumbar or sacral, single facet joint
64636	Destruction by neurolytic agent, paravertebral facet joint nerve(s), with imaging guidance (fluoroscopy or CT); lumbar or sacral, each additional facet joint
76942	Ultrasonic guidance for needle placement (eg, biopsy, aspiration, injection, localization device), imaging supervision and interpretation
77002	Fluoroscopic guidance for needle placement (eg, biopsy, aspiration, injection, localization device), imaging supervision and interpretation
77003	Fluoroscopic guidance and localization of needle or catheter tip for spine or paraspinous diagnostic or therapeutic injection procedures (epidural or subarachnoid)
77021	Magnetic resonance guidance for needle placement (eg, for biopsy, needle aspiration, injection, or placement of localization device) radiological supervision and interpretation
96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
HCPCS Codes	
M0076	Prolotherapy
S2348	Decompression procedure, percutaneous, of nucleus pulposus of intervertebral disc, using radiofrequency energy, single or multiple levels, lumbar

Note: Inclusion on this list does not guarantee coverage

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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.

CG – Management of Chronic Otitis Media with Effusion in Children

Question: How should the HERC approved Coverage Guidance – Management of chronic otitis media with effusion in children—be incorporated into the Prioritized List?

Question source: Health Evidence Review Commission

Issue: HERC approved the Coverage Guidance: Management of chronic otitis media with effusion in children in October, 2012. This coverage guidance needs to be evaluated for application within the Prioritized List.

At the December 2012 VBBS meeting testimony was heard and a discussion to make modifications to the proposed guideline followed. The proposal had recommended striking language including the definition of 25dB hearing loss, and the decision was made to leave this language as part of the guideline. Additionally, the “individualized” treatment language was not operationalizable by DMAP and so the proposal was to add tympanostomy tubes to those specified underlying condition lines (e.g. Down syndrome, cleft palate, and craniofacial anomalies). It was decided not to add these codes to the speech and language delay lines because these are dysfunction lines.

HERC Coverage Guidance

Antibiotic and other medication therapy (including antihistamines, decongestants, and nasal steroids) should not be covered for children with children with otitis media with effusion (OME) (without another appropriate diagnosis).

There should be a 3 to 6 month watchful waiting period after diagnosis of otitis media with effusion, and if documented persistent hearing loss is greater than or equal to 25dB in the better hearing ear, referral for tympanostomy surgery may be covered, given short, but not long-term, improvement in hearing.

Formal audiometry should be covered 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 covered initially upon diagnosis. Children with chronic OME who are not at risk for language 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 should not be covered at the time of the first pressure equalization tube insertion.

Patients with craniofacial anomalies, Down’s syndrome, cleft palate, and patients with speech and language delay along with hearing loss should have coverage based on an individualized treatment plan.

CG – Management of Chronic Otitis Media with Effusion in Children

Current Prioritized List status: chronic otitis media is included on line 502 CHRONIC OTITIS MEDIA Treatment: PE TUBES/ADENOIDECTOMY/TYMPANOPLASTY, MEDICAL THERAPY. Currently, guideline note 51 applies to this line.

Line: 502
Condition: CHRONIC OTITIS MEDIA (See Guideline Notes 51,64,65,76)
Treatment: PE TUBES/ADENOIDECTOMY/TYMPANOPLASTY, MEDICAL THERAPY
ICD-9: 380.50-380.53,381.10-381.89,382.1-382.3,382.9,383.1,383.20-383.31,383.9,384.20-384.9
CPT: 42830-42836,69210-69222,69310,69400-69511,69601-69650,69700,69801,69905,69910,69979,92562-92565,92571-92577,92590,92591,98966-98969,99051,99060,99070,99078,99201-99360,99366,99374,99375,99379-99412,99429-99444,99468-99480,99605-99607
HCPCS: G0396,G0397,G0406-G0408,G0425-G0427,S0270-S0274

GUIDELINE NOTE 51, CHRONIC OTITIS MEDIA WITH EFFUSION

Line 502

Antibiotic and other medication therapy are not indicated for children with chronic otitis media with effusion (OME). Children with chronic OME present for 3 months or longer or with language delay, learning problems, or significant hearing loss at any time should have hearing testing. Children with chronic OME who are not at risk 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.

For the child who has had chronic OME and who has a hearing deficiency in the better-hearing ear of 25 dB or greater, myringotomy with tube insertion recommended after a total of 4 to 6 months of effusion with a documented hearing deficit.

Adenoidectomy is an appropriate surgical treatment for chronic OME in children over 3 years with their second set of tubes. First time tubes are not an indication for an adenoidectomy.

CG – Management of Chronic Otitis Media with Effusion in Children

Code	Line	Condition	Treatment	Staff REcommendation
749.00	49	CONGENITAL AIRWAY OBSTRUCTION WITH OR WITHOUT CLEFT PALATE	MEDICAL AND SURGICAL TREATMENT, ORTHODONTICS	Do not add tympanostomy codes to this line because about airway obstruction.
749.00	325	CLEFT PALATE AND/OR CLEFT LIP	EXCISION AND REPAIR VESTIBULE OF MOUTH, ORTHODONTICS	Add tympanostomy codes
756.0	273	DEFORMITIES OF HEAD	CRANIOTOMY/CRANIECTOMY	Do not add codes to this line

Down syndrome is located on the dysfunction lines, as well as speech and language delay is located on dysfunction line 375. These are not ideal locations for adding tympanostomy codes.

HERC Staff Recommendations:

1. Make the following changes to Guideline Note 51

GUIDELINE NOTE 51, CHRONIC OTITIS MEDIA WITH EFFUSION

Lines [325](#), [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](#)).

[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](#) cChildren with chronic OME present for 3 months or longer. ~~or~~ [Children](#) with language delay, learning problems, or significant hearing loss ~~at any time~~ 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~~ ~~is an appropriate surgical treatment for~~

CG – Management of Chronic Otitis Media with Effusion in Children

~~chronic OME~~ in children over 3 years ~~with~~ who are having their second set of tubes. ~~First time tubes are not an indication for an adenoidectomy.~~

Patients with craniofacial anomalies, Down's syndrome, and cleft palate, or documented speech and language delay along with hearing loss and chronic otitis media with effusion are intended to have coverage through the co-morbidity rule.

2. Add the following cpt codes to Line 325 CLEFT PALATE AND/OR CLEFT LIP
 - 69433 Tympanostomy (requiring insertion of ventilating tube, local or topical anesthesia)
 - 69436 Tympanostomy (requiring insertion of ventilating tube, general anesthesia)
 - 69424 Ventilating tube removal requiring general anesthesia

Comorbidity Rule

ORS 410-141-0480

Oregon Health Plan Benefit Package of Covered Services

(1) Division members are eligible to receive, subject to Section (11) of this rule, those treatments for the condition/treatment pairs funded on the Oregon Health Services Commission's (HSC) Prioritized List of Health Services adopted under OAR 410-141-0520 when such treatments are medically or dentally appropriate, except that services must also meet the prudent layperson standard defined in OAR 410-141-0140. Refer to 410-141-0520 for funded line coverage information.

(8) In addition to the coverage available under section (1) of this rule, a Division member may be eligible to receive, subject to section (11), services for treatments that are below the funded line or not otherwise excluded from coverage:

(a) Services can be provided if it can be shown that:

(A) The OHP client has a funded condition for which documented clinical evidence shows that the funded treatments are not working or are contraindicated; and

(B) Concurrently has a medically related unfunded condition that is causing or exacerbating the funded condition; and

(C) Treating the unfunded medically related condition would significantly improve the outcome of treating the funded condition;

(D) Ancillary services that are excluded and other services that are excluded are not subject to consideration under this rule;

(E) Any unfunded or funded co-morbid conditions or disabilities must be represented by an ICD-9-CM diagnosis code or when the condition is a mental disorder, represented by DSM-IV diagnosis coding to the highest level of axis specificity; and

(F) In order for the treatment to be covered, there must be a medical determination and finding by the Division for fee-for-service OHP clients or a finding by the Prepaid Health Plan (PHP) for Division members that the terms of section (a)(A)–(C) of this rule have been met based upon the applicable:

(i) Treating physician opinion;

(ii) Medical research;

(iii) Community standards; and

(iv) Current peer review.

(b) Before denying treatment for an unfunded condition for any Division member, especially a Division member with a disability or with a co-morbid condition, providers must determine whether the Division member has a funded condition/treatment pair that would entitle the Division member to treatment under the program and both the funded and unfunded conditions must be represented by an ICD- 9-CM diagnosis code; or, when the condition is a mental disorder, represented by DSM-IV diagnosis coding to the highest level of axis specificity.

Section 7

Guidelines

Immunization Guideline

Question: Should the current Prevention Tables have immunization recommendations removed and placed into a separate table to be maintained by the Oregon Immunization Program?

Question source: HERC staff, Oregon Immunization Program staff

Issue: The current Prevention Tables are out of date, and are not scheduled to be replaced until the ICD-10 List in 2014. The immunization recommendations in these tables are out of date, and not regularly updated. The Oregon Immunization Program has proposed having an updated table to be hosted by OIP and regularly updated by their staff. This table will be available through a link in a new Prioritized List guideline.

Traditionally, HSC/HERC has followed ACIP immunization recommendations, which are created by public health experts and the CDC. The OIP program follows ACIP guidelines.

If the following guideline referring to the OIP table is adopted, then changes will need to be made to the Prevention Tables as shown below.

Recommendations:

- 1) Adopt the guideline regarding immunizations as shown below
 - a. The link is to a table to be regularly updated by the Oregon Immunization Program (see second document)
- 2) Accept the changes to the Prevention Tables as shown below

GUIDELINE NOTE XXX IMMUNIZATIONS

Lines 3,4

Immunizations are covered as recommended in the following table. The immunization table is updated and maintained on this website

<http://public.health.oregon.gov/PreventionWellness/VaccinesImmunization/ImmunizationProviderResources/Documents/DMAPvactable.pdf>

Immunization Guideline

Birth to 10 Years

Interventions Considered and Recommended for the Periodic Health Examination

Leading Causes of Death

Conditions originating in perinatal period
Congenital anomalies
Sudden infant death syndrome (SIDS)
Unintentional injuries (non-motor vehicle)
Motor vehicle injuries

Interventions for the General Population

SCREENING

Height and weight
Blood pressure
Vision screen (3-4 yr)
Hemoglobinopathy screen (birth)¹
Phenylalanine level (birth)²
T4 and/or TSH (birth)³
Effects of STDs
FAS, FAE, drug affected infants⁴
Hearing, developmental, behavioral and/or psychosocial screens⁵
Learning and attention disorders⁶
Signs of child abuse, neglect, family violence

Limit fat and cholesterol; maintain caloric balance; emphasize grains, fruits, vegetables (age >2 yr)
Regular physical activity*

Substance User

Effects of passive smoking*
Anti-tobacco message*

Dental Health

Regular visits to dental care provider*
Floss, brush with fluoride toothpaste daily*
Advice about baby bottle tooth decay*

COUNSELING

Injury Prevention

Child safety car seats (age <5 yr)
Lap-shoulder belts (age >5 yr)
Bicycle helmet; avoid bicycling near traffic
Smoke detector, flame retardant sleepwear
Hot water heater temperature <120-130F
Window/stair guards, pool fence, walkers
Safe storage of drugs, toxic substances, firearms and matches
Syrup of ipecac, poison control phone number
CPR training for parents/caretakers
Infant sleeping position

Mental Health/Chemical Dependency

Parent education regarding:

- Child development
- Attachment/bonding
- Behavior management
- Effects of excess TV watching
- Special needs of child and family due to:
 - Familial stress or disruption
 - Health problems
 - Temperamental incongruence with parent
 - Environmental stressors such as community violence or disaster, immigration, minority status, homelessness
- Referral for MHCD and other family support services as indicated

Diet and Exercise

Breast-feeding, iron-enriched formula and foods (infants and toddlers)

¹Whether screening should be universal or targeted to high-risk groups will depend on the proportion of high-risk individuals in the screening area, and other considerations. ²If done during first 24 hr of life, repeat by age 2 wk. ³Optimally between day 2 and 6, but in all cases before newborn nursery discharge. ⁴Parents with alcohol and/or drug use. Children with history of intrauterine addiction. Physical and behavioral indicators: hypertension, gastritis, esophagitis, hematological disorders, poor nutritional status, cardiac arrhythmias, neurological disorders, intrauterine growth retardation, mood swings, difficulty concentrating, inappropriateness, irritability or agitation, depression, bizarre behavior, abuse and neglect, behavior problems. ⁵Screening must be conducted with a standardized, valid, and reliable tool. Recommended developmental, behavioral and/or psychosocial screening tools include and are not limited to: a) Ages and Stages Questionnaire (ASQ); b) Parent Evaluation of Developmental Status, (PEDS) plus/minus PEDS:Developmental Milestones (PEDS:DM); c) ASQ:Social Emotional (ASQ:SE); and d) Modified Checklist for Autism in Toddlers (M-CHAT). ⁶Consider screening with full DSM-IV criteria for attention deficit disorder, inattentive or hyperactive types, in children with significant overall academic or behavioral difficulty including academic failure and/or learning difficulty, especially in reading, math or handwriting.

*The ability of clinical counseling to influence this behavior is unproven.

Immunization Guideline

Birth to 10 Years (Cont'd)

Interventions for the General Population (Cont'd)

IMMUNIZATIONS

Diphtheria-tetanus-acellular-pertussis (DTaP)
Inactivated poliovirus (OPV)
Measles-mumps-rubella (MMR)
H. influenzae type b (Hib) conjugate
Hepatitis B
Varicella
Pneumococcal

Hepatitis A
Influenza
Rotavirus
Human papillomavirus (HPV)

CHEMOPROPHYLAXIS

Ocular prophylaxis (birth)

~~HPV2 and HPV4 for females aged 9 to 26. HPV4 for males aged 9 through 26.~~

Interventions for the High-Risk Population

Hemoglobin/hematocrit (HR1)
HIV testing (HR2)
PPD (HR3)
~~Hepatitis A vaccine (HR4);~~
~~Pneumococcal polysaccharide vaccine (HR5)~~
~~Meningococcal vaccine (HR6)~~
Blood lead level (HR7)

Daily fluoride supplement (HR8)
Avoid excess/midday sun, use protective clothing* (HR9)
Screen for child abuse, neurological, mental health conditions
Increased well-child visits (HR10)

High-Risk Groups

HR1 = Infants age 6-12 mo who are: living in poverty, black, Native American or Alaska Native, immigrants from developing countries, preterm and low-birthweight infants, infants whose principal dietary intake is unfortified cow's milk.

HR2 = Infants born to high-risk mothers whose HIV status is unknown. Women at high risk include: past or present injection drug use; persons who exchange sex for money or drugs, and their sex partners; injection drug-using, bisexual, or HIV-positive sex partners currently or in past; persons seeking treatment for STDs; blood transfusion during 1978-1985.

HR3 = Persons infected with HIV, close contacts of persons with known or suspected TB, persons with medical risk factors associated with TB, immigrants from countries with high TB prevalence, medically underserved low-income populations (including homeless), residents of long-term care facilities.

~~**HR4** = Persons >2 yr living in areas where the disease is endemic and where periodic outbreaks occur (e.g., certain Alaska Native, Pacific Island, Native American, and religious communities). Consider for institutionalized children aged >2 yr. Clinicians should also consider local epidemiology.~~

~~**HR5** = Children aged 2 years or older with certain underlying medical conditions, including a cochlear implant.~~

~~**HR6** = Children aged 2 through 10 years with persistent complement component deficiency, anatomic or functional asplenia, and certain other conditions placing them at high risk.~~

Immunization Guideline

HR74 = Children about age 12 mo who: 1) live in communities in which the prevalence of lead levels requiring individual intervention, including residential lead hazard control or chelation, is high or undefined; 2) live in or frequently visit a home built before 1950 with dilapidated paint or with recent or ongoing renovation or remodeling; 3) have close contact with a person who has an elevated lead level; 4) live near lead industry or heavy traffic; 5) live with someone whose job or hobby involves lead exposure; 6) use lead-based pottery; or 7) take traditional ethnic remedies that contain lead.

HR85 = Children living in areas with inadequate water fluoridation (<0.6 ppm).

HR96 = Persons with a family history of skin cancer, a large number of moles, atypical moles, poor tanning ability, or light skin, hair, and eye color.

HR107 = Having a: chronically mentally ill parent; substance abusing parent; mother who began parenting as a teen. Living at or below poverty. Having: parents involved in criminal behavior; experienced an out-of-home placement(s), multiple moves, failed adoption(s). Being homeless. Having suffered physical, emotional or sexual abuse, or severe neglect. Having: a chronic health problem in the family; an absence of a family support system. Being substance affected at birth.

Immunization Guideline

Ages 11-24 Years

Interventions Considered
and Recommended for the
Periodic Health Examination

Leading Causes of Death
Motor vehicle/other unintentional injuries
Homicide
Suicide
Malignant neoplasms
Heart diseases

Interventions for the General Population

SCREENING

Height and weight
Blood pressure¹
High-density lipoprotein cholesterol (HDL-C) and
total blood cholesterol (age 20-24 if high-risk)²
Papanicolaou (Pap) test³
Chlamydia screen⁴ (females <25 yr)
Rubella serology or vaccination hx⁵
(females >12 yr)
Learning and attention disorders⁶
Signs of child abuse, neglect, family violence
Alcohol, inhalant, illicit drug use⁷
Eating disorders⁸
Anxiety and mood disorders⁹
Suicide risk factors¹⁰

COUNSELING

Injury Prevention

Lap/shoulder belts
Bicycle/motorcycle/ATV helmet*
Smoke detector*
Safe storage/removal of firearms*
Smoking near bedding or upholstery

Substance Use

Avoid tobacco use
Avoid underage drinking and illicit drug use*
Avoid alcohol/drug use while driving, swimming,
boating, etc.*

Sexual Behavior

STD prevention: abstinence*; avoid high-risk
behavior*; condoms/female barrier with spermicide*
Unintended pregnancy: contraception

Diet and Exercise

Limit fat and cholesterol; maintain caloric
balance; emphasize grains, fruits, vegetables
Adequate calcium intake (females)
Regular physical activity*

Dental Health

Regular visits to dental care provider*
Floss, brush with fluoride toothpaste daily*

Mental Health/Chemical Dependency

Parent education regarding:

- Adolescent development
- Behavior management
- Effects of excess TV watching
- Special needs of child and family due to:
 - Familial stress or disruption
 - Health problems
 - Temperamental incongruence with parent
 - Environmental stressors such as
community violence or disaster,
immigration, minority status,
..homelessness
- Referral for MHCD and other family support
services as indicated

¹Periodic BP for persons aged ≥ 18 yr. ²High-risk defined as having diabetes, family history of premature coronary disease or familial hyperlipidemia, or multiple cardiac risk factors. ³Screening to start at age 21; screening should occur at least every 3 years. ⁴If sexually active. ⁵Serologic testing, documented vaccination history, and routine vaccination against rubella (preferably with MMR) are equally acceptable alternatives. ⁶Consider screening with full DSM-IV criteria for attention deficit disorder, inattentive or hyperactive types, in children with significant overall academic or behavioral difficulty including academic failure and/or learning difficulty, especially in reading, math or handwriting. ⁷Persons using alcohol and/or drugs. Physical and behavioral indicators: liver disease, pancreatitis, hypertension, gastritis, esophagitis, hematological disorders, poor nutritional status, cardiac arrhythmias, alcoholic myopathy, ketoacidosis, neurological disorders: smell of alcohol on breath, mood swings, memory lapses or losses, difficulty concentrating, blackouts, inappropriateness, irritability or agitation, depression, slurry speech, staggering gait, bizarre behavior, suicidal indicators, sexual dysfunction, interpersonal conflicts, domestic violence, child abuse and neglect, automobile accidents or citation arrests, scholastic or behavior problems, secretiveness or vagueness about personal or medical history. ⁸Persons with a weight >10% below ideal body weight, parotid gland hypertrophy or erosion of tooth enamel. Females with a chemical dependency. ⁹In women who are at increased risk, diagnostic evaluation should include an assessment of history of sexual and physical violence, interpersonal difficulties, prescription drug utilization, medical and reproductive history. ¹⁰Recent divorce, separation, unemployment, depression, alcohol or other drug abuse, serious medical illness, living alone, homelessness, or recent bereavement.

*The ability of clinical counseling to influence this behavior is unproven.

Immunization Guideline

Ages 11-24 Years (Cont'd)

Interventions for the General Population (Cont'd)

IMMUNIZATIONS

TDaP (11-16-yr)
Hepatitis B¹
MMR (11-12-yr)²
Varicella (11-12-yr)³
Rubella⁴ (females >12-yr)
Influenza⁵

Polio⁶
Human papillomavirus (HPV)⁷
Meningococcal (11-12-yr)⁸

CHEMOPROPHYLAXIS

Multivitamin with folic acid (females planning/capable of pregnancy)

If not previously immunized: current visit, 1 and 6 mo later. ²If no previous second dose of MMR. ³If susceptible to chickenpox. ⁴Serologic testing, documented vaccination history, and routine vaccination against rubella (preferably with MMR) are equally acceptable alternatives. ⁵Yearly (6 mo through 18 yrs). ⁶If not previously immunized. ⁷HPV² and HPV⁴ for females aged 9 to 26. HPV⁴ for males aged 9 through 26. ⁸Children 13 through 18 if not previously vaccinated.

Interventions for the High-Risk Population

Screen for

Syphilis RPR/VDRL (HR1);
Gonorrhea (female) (HR2)
HIV (HR3)
Chlamydia (female) (HR4);
Tuberculosis - PPD (HR3,5)

Advise to reduce infection risk (HR3,6)

Immunize with

~~MMR (HR12)~~
~~Hepatitis A vaccine (HR7)~~
~~Meningococcal vaccine (HR7)~~
~~Pneumococcal polysaccharide vaccine (HR8)~~
~~Influenza vaccine (HR9)~~
~~Varicella vaccine (HR10)~~

~~MMR (HR12)~~

~~Hepatitis A vaccine (HR7)~~

Avoid excess/midday sun, use protective clothing* (HR~~12~~7)

Folic acid 4.0 mg (HR~~13~~8)

Daily fluoride supplement (HR~~14~~9)

Screen for child abuse, neurological, mental health conditions

Increased well-child/adolescent visits (HR~~15~~10)

Refer for genetic counseling and evaluation for BRCA testing by appropriately trained health care provider (HR~~16~~11).

High-Risk Groups

HR1 = Persons who exchange sex for money or drugs, and their sex partners; persons with other STDs (including HIV); and sexual contacts of persons with active syphilis. Clinicians should also consider local epidemiology.

HR2 = Females who have: two or more sex partners in the last year; a sex partner with multiple sexual contacts; exchanged sex for money or drugs; or a history of repeated episodes of gonorrhea. Clinicians should also consider local epidemiology.

Immunization Guideline

Ages 11-24 Years (Cont'd)

HR3 = Males who had sex with males after 1975; past or present injection drug use; persons who exchange sex for money or drugs, and their sex partners; injection drug-using, bisexual or HIV-positive sex partner currently or in the past; blood transfusion during 1978-85; persons seeking treatment for STDs. Clinicians should also consider local epidemiology.

HR4 = Sexually active females with multiple risk factors including: history of prior STD; new or multiple sex partners; age < 25; nonuse or inconsistent use of barrier contraceptives; cervical ectopy. Clinicians should consider local epidemiology of the disease in identifying other high-risk groups.

HR5 = HIV positive, close contacts of persons with known or suspected TB, persons with medical risk factors associated with TB, immigrants from countries with high TB prevalence, medically underserved low-income populations (including homeless), alcoholics, injection drug users, and residents of long-term facilities.

HR6 = Persons who continue to inject drugs.

~~**HR7** = Children aged 11 through 12 years with persistent complement component deficiency, anatomic or functional asplenia, and certain other conditions placing them at high risk.~~

~~**HR8** = Immunocompetent persons with certain medical conditions, including chronic cardiopulmonary disorders, diabetes mellitus, and anatomic asplenia. Immunocompetent persons who live in high-risk environments/social settings (e.g., certain Native American and Alaska Native populations).~~

~~**HR9** = Annual vaccination of: residents of chronic care facilities; persons with chronic cardiopulmonary disorders, metabolic diseases (including diabetes mellitus); hemoglobinopathies, immunosuppression, or renal dysfunction.~~

~~**HR10** = Healthy persons aged >13 yr without a history of chickenpox or previous immunization. Consider serologic testing for presumed susceptible persons aged >13 yr.~~

~~**HR11** = Persons born after 1956 who lack evidence of immunity to measles or mumps (e.g., documented receipt of live vaccine on or after the first birthday, laboratory evidence of immunity, or a history of physician-diagnosed measles or mumps).~~

HR127 = Persons with a family or personal history of skin cancer, a large number of moles, atypical moles, poor tanning ability, or light skin, hair, and eye color.

HR138 = Women with prior pregnancy affected by neural tube defect planning a pregnancy.

Immunization Guideline

Ages 11-24 Years (Cont'd)

HR149 = Persons aged <17 yr living in areas with inadequate water fluoridation (<0.6 ppm).

HR150 = Having a: chronically mentally ill parent; substance abusing parent; mother who began parenting as a teen. Living at or below poverty. Having: parents involved in criminal behavior; experienced an out-of-home placement(s), multiple moves, failed adoption(s). Being homeless. Having suffered physical, emotional or sexual abuse, or severe neglect. Having: a chronic health problem in the family; an absence of a family support system. Being substance affected at birth.

HR161 = A family history of breast or ovarian cancer that includes a relative with a known deleterious mutation in BRCA1 or BRCA2 genes; two first-degree relatives with breast cancer, one of whom received the diagnosis at age 50 years or younger; a combination of three or more first- or second-degree relatives with breast cancer regardless of age at diagnosis; a combination of both breast and ovarian cancer among first- and second-degree relatives; a first-degree relative with bilateral breast cancer; a combination of two or more first- or second-degree relatives with ovarian cancer regardless of age at diagnosis; a first- or second-degree relative with both breast and ovarian cancer at any age; and a history of breast cancer in a male relative. For women of Ashkenazi Jewish heritage, an increased risk family history risk includes any first-degree relative (or two second-degree relatives on the same side of the family) with breast or ovarian cancer.

Immunization Guideline

Ages 25-64 Years

Interventions Considered
and Recommended for the
Periodic Health Examination

Leading Causes of Death
Malignant neoplasms
Heart diseases
Motor vehicle/other unintentional injuries
Human immunodeficiency virus infection
Suicide and homicide

Interventions for the General Population

SCREENING

Blood pressure
Height and weight
High-density lipoprotein cholesterol (HDL-C) and total blood cholesterol (men age 35-64, women age 45-64, all age 25-64 if high-risk¹)
Papanicolaou (Pap) test²
Fecal occult blood test (FOBT) and/or flexible sigmoidoscopy, or colonoscopy (>50 yr)³
Mammogram⁵ (women 40-74 yrs)
Rubella serology or vaccination hx⁵ (women of childbearing age)
Bone density measurement (women age 60-64 if high-risk)⁶
Fasting plasma glucose for patients with hypertension or hyperlipidemia
Learning and attention disorders⁷
Signs of child abuse, neglect, family violence
Alcohol, inhalant, illicit drug use⁸
Eating disorders⁹
Anxiety and mood disorders¹⁰
Suicide risk factors¹¹
Somatoform disorders¹²
Environmental stressors¹³

COUNSELING

Substance Use

Tobacco cessation
Avoid alcohol/drug use while driving, swimming, boating, etc.*

Diet and Exercise

Limit fat and cholesterol; maintain caloric balance; emphasize grains, fruits, vegetables
Adequate calcium intake (women)
Regular physical activity*

Injury Prevention

Lap/shoulder belts
Bicycle/motorcycle/ATV helmet*
Smoke detector*
Safe storage/removal of firearms*
Smoking near bedding or upholstery

Sexual Behavior

STD prevention: abstinence*; avoid high-risk behavior*; condoms/female barrier with spermicide*
Unintended pregnancy: contraception

Dental Health

Regular visits to dental care provider*
Floss, brush with fluoride toothpaste daily*

IMMUNIZATIONS

Tdap boosters¹⁴
Human papillomavirus (HPV)¹⁵
Rubella⁵ (women of childbearing age)
Zoster (60 or older)

CHEMOPROPHYLAXIS

Multivitamin with folic acid (females planning or capable of pregnancy)
Discuss aspirin prophylaxis for those at high-risk for coronary heart disease

¹High-risk defined as having diabetes, family history of premature coronary disease or familial hyperlipidemia, or multiple cardiac risk factors. ²Women who are or have been sexually active and who have a cervix: q < 3 yr. ³FOBT: annually; flexible sigmoidoscopy: every 5 years; colonoscopy: every 10 years. ⁴The screening decision for women 40-49 should be a mutual decision between a woman and her clinician. If a decision to proceed with mammography is made, it should be done every 2 years. ⁵Between the ages of 50-74, screening mammography should be performed every 2 years. ⁶Serologic testing, documented vaccination history, and routine vaccination (preferably with MMR) are equally acceptable. ⁷High-risk defined as weight <70kg, not on estrogen replacement. ⁸Consider screening with full DSM-IV criteria for attention deficit disorder, inattentive or hyperactive types, in children with significant overall academic or behavioral difficulty including academic failure and/or learning difficulty, especially in reading, math or handwriting. ⁹Persons using alcohol and/or drugs. Physical and behavioral indicators: liver disease, pancreatitis, hypertension, gastritis, esophagitis, hematological disorders, poor nutritional status, cardiac arrhythmias, alcoholic myopathy, ketoacidosis, neurological disorders: smell of alcohol on breath, mood swings, memory lapses or losses, difficulty concentrating, blackouts, inappropriateness, irritability or agitation, depression, slurry speech, staggering gait, bizarre behavior, suicidal indicators, sexual dysfunction, interpersonal conflicts, domestic violence, child abuse and neglect, automobile accidents or citation arrests, scholastic or behavior problems, secretiveness or vagueness about personal or medical history. ¹⁰Persons with a weight >10% below ideal body weight, parotid gland hypertrophy or erosion of tooth enamel. Females with a chemical dependency. ¹¹In women who are at increased risk, diagnostic evaluation should include an assessment of history of sexual and physical violence, interpersonal difficulties, prescription drug utilization, medical and reproductive history. ¹²Recent divorce, separation, unemployment, depression, alcohol or other drug abuse, serious medical illness, living alone, homelessness, or recent bereavement. ¹³Multiple unexplained somatic complaints. ¹⁴Community violence or disaster, immigration, homelessness, family medical problems. ¹⁵One-time Tdap dose to

Immunization Guideline

~~substitute for Td booster; then boost with Td every 10 years. ⁴⁵HPV2 and HPV4 for women aged 19 through 26. Discussion with provider regarding HPV4 for males aged 19 through 26.~~

*The ability of clinical counseling to influence this behavior is unproven.

Immunization Guideline

Ages 25-64 Years (Cont'd)

Interventions for the High-Risk Population

RPR/VDRL (HR1); screen for gonorrhea (female) (HR2), HIV (HR3), chlamydia (female) (HR4);

PPD (HR75)
advice to reduce Infection risk (HR86)

~~Hepatitis B vaccine (HR5); Hepatitis A vaccine (HR6); pneumococcal polysaccharide vaccine (HR9); influenza vaccine (HR10); MMR (HR11); varicella~~

~~—vaccine, (HR12); meningococcal vaccine (HR16)~~

Avoid excess/midday sun, use protective clothing* (HR137)

Folic acid 4.0 mg (HR148)

Refer for genetic counseling and evaluation for BRCA testing by appropriately trained health care provider (HR159)

High Risk Groups

HR1 = Persons who exchange sex for money or drugs, and their sex partners; persons with other STDs (including HIV); and sexual contacts of persons with active syphilis. Clinicians should also consider local epidemiology.

HR2 = Women who exchange sex for money or drugs, or who have had repeated episodes of gonorrhea. Clinicians should also consider local epidemiology.

HR3 = Males who had sex with males after 1975; past or present injection drug use; persons who exchange sex for money or drugs, and their sex partners; injection drug-using, bisexual or HIV-positive sex partner currently or in the past; blood transfusion during 1978-1985; persons seeking treatment for STDs. Clinicians should also consider local epidemiology.

HR4 = Sexually active women with multiple risk factors including: history of STD; new or multiple sex partners; nonuse or inconsistent use of barrier contraceptives; cervical ectopy. Clinicians should consider local epidemiology.

~~**HR5** = Blood product recipients (including hemodialysis patients), men who have sex with men, injection drug users and their sex partners, persons with multiple recent sex partners, persons with other STDs (including HIV).~~

~~**HR6** = Persons living in areas where the disease is endemic and where periodic outbreaks occur (e.g., certain Alaska Native, Pacific Island, Native American, and religious communities); men who have sex with men; injection or street drug users. Consider for institutionalized persons. Clinicians should also consider local epidemiology.~~

Immunization Guideline

Ages 25-64 Years (Cont'd)

HR75 = HIV positive, close contacts of persons with known or suspected TB, persons with medical risk factors associated with TB, immigrants from countries with high TB prevalence, medically underserved low-income populations (including homeless), alcoholics, injection drug users, and residents of long-term facilities.

HR86 = Persons who continue to inject drugs.

~~**HR9** = Immunocompetent institutionalized persons >50-yr and immunocompetent with certain medical conditions, including chronic cardiac or pulmonary disease, diabetes mellitus, and anatomic asplenia. Immunocompetent persons who live in high-risk environments or social settings (e.g., certain Native American and Alaska Native populations).~~

~~**HR10** = Annual vaccination of residents of chronic care facilities; persons with chronic cardiopulmonary disorders, metabolic diseases (including diabetes mellitus), hemoglobinopathies, immunosuppression or renal dysfunction.~~

~~**HR11** = Persons born after 1956 who lack evidence of immunity to measles or mumps (e.g., documented receipt of live vaccine on or after the first birthday, laboratory evidence of immunity, or a history of physician-diagnosed measles or mumps).~~

~~**HR12** = Healthy adults without a history of chickenpox or previous immunization. Consider serologic testing for presumed susceptible adults.~~

HR137 = Persons with a family or personal history of skin cancer, a large number of moles, atypical moles, poor tanning ability, or light skin, hair, and eye color.

HR148 = Women with previous pregnancy affected by neural tube defect who are planning pregnancy.

HR159 = A family history of breast or ovarian cancer that includes a relative with a known deleterious mutation in BRCA1 or BRCA2 genes; two first-degree relatives with breast cancer, one of whom received the diagnosis at age 50 years or younger; a combination of 3 or more first- or second-degree relatives with breast cancer regardless of age at diagnosis; a combination of both breast and ovarian cancer among first- and second-degree relatives; a first-degree relative with bilateral breast cancer; a combination of two or more first- or second-degree relatives with ovarian cancer regardless of age at diagnosis; a first- or second-degree relative with both breast and ovarian cancer at any age; and a history of breast cancer in a male relative. For women of Ashkenazi Jewish heritage, an increased risk family history risk includes any first-degree relative (or two second-degree relatives on the same side of the family) with breast or ovarian cancer.

~~**HR16** = Adults with anatomic or functional asplenia or persistent complement component deficiencies; first-year college students living in dormitories, military recruits~~

Immunization Guideline

Age 65 and Older

Interventions Considered
and Recommended for the
Periodic Health Examination

Leading Causes of Death
Heart diseases
Malignant neoplasms (lung, colorectal,
breast)
Cerebrovascular disease
Chronic obstructive pulmonary disease
Pneumonia and influenza

Interventions for the General Population

SCREENING

Blood pressure
Height and weight
Fecal occult blood test (FOBT) and/or flexible
sigmoidoscopy or colonoscopy t.¹
Mammogram (women ages 65-74)²
Bone density measurement (women)
Fasting plasma glucose for patients with hypertension or
hyperlipidemia
Vision screening
Assess for hearing impairment
Signs of elder abuse, neglect, family violence
Alcohol, inhalant, illicit drug use³
Anxiety and mood disorders⁴
Somatoform disorders⁵
Environmental stressors⁶
Abdominal aortic aneurysm (AAA) (men aged 65 to 75 who
have ever smoked)⁷

COUNSELING

Substance Use

Tobacco cessation
Avoid alcohol/drug use while driving, swimming,
boating, etc.*

Diet and Exercise

Limit fat and cholesterol; maintain caloric
balance; emphasize grains, fruits, vegetables
Adequate calcium intake (women)
Regular physical activity*

Assess eating environment

Injury Prevention

Lap/shoulder belts
Motorcycle and bicycle helmets*
Fall prevention*
Safe storage/removal of firearms*
Smoke detector*
Set hot water heater to <120-130°F
CPR training for household members
Smoking near bedding or upholstery

Dental Health

Regular visits to dental care provider*
Floss, brush with fluoride toothpaste daily*
Sexual Behavior
STD prevention: avoid high-risk sexual behavior*;
use condoms

IMMUNIZATIONS

Pneumococcal vaccine
Influenza*
Tetanus-diphtheria (Td)-boosters
Zoster vaccine

CHEMOPROPHYLAXIS

Discuss aspirin prophylaxis for those at high-risk
for coronary heart disease

¹FOBT: annually; flexible sigmoidoscopy: every 5 years; colonoscopy: every 10 years through age 75. ²Screening mammography should be performed every 2 years. ³Persons using alcohol and/or drugs. Physical and behavioral indicators: liver disease, pancreatitis, hypertension, gastritis, esophagitis, hematological disorders, poor nutritional status, cardiac arrhythmias, alcoholic myopathy, ketoacidosis, neurological disorders: smell of alcohol on breath, mood swings, memory lapses or losses, difficulty concentrating, blackouts, inappropriateness, irritability or agitation, depression, slurry speech, staggering gait, bizarre behavior, suicidal indicators, sexual dysfunction, interpersonal conflicts, domestic violence, child abuse and neglect, automobile accidents or citation arrests, scholastic or behavior problems, secretiveness or vagueness about personal or medical history. ⁴In women who are at increased risk, diagnostic evaluation should include an assessment of history of sexual and physical violence, interpersonal difficulties, prescription drug utilization, medical and reproductive history. ⁵Multiple unexplained somatic complaints. ⁶Community violence or disaster, immigration, homelessness, family medical problems. ⁷One-time ultrasound. *Annually.

*The ability of clinical counseling to influence this behavior is unproven

Immunization Guideline

Age 65 and Older (Cont'd)

Interventions for the High-Risk Population

PPD (HR1); amantadine/rimantadine (HR4)	HIV screen (HR3); hepatitis B vaccine (HR8) RPR/VDRL (HR9)
Fall prevention intervention (HR5) Consider cholesterol screening (HR6) Avoid excess/midday sun, use protective clothing* (HR7); hepatitis A vaccine (HR2)	Advice to reduce Infection risk (HR10) Varicella vaccine (HR11) Refer to meal and social support resources Refer for genetic counseling and evaluation for BRCA testing by appropriately trained health care provider (HR12)

High Risk Groups

HR1 = HIV positive, close contacts of persons with known or suspected TB, persons with medical risk factors associated with TB, immigrants from countries with high TB prevalence, medically underserved low-income populations (including homeless), alcoholics, injection drug users, and residents of long-term facilities.

~~**HR2** = Persons living in areas where the disease is endemic and where periodic outbreaks occur (e.g., certain Alaska Native, Pacific Island, Native American, and religious communities); men who have sex with men; injection or street drug users. Consider for institutionalized. Clinicians should also consider local epidemiology.~~

HR3 = Men who had sex with males after 1975; past or present injection drug use; persons who exchange sex for money or drugs, and their sex partners; injection drug-using, bisexual or HIV-positive sex partner currently or in the past; blood transfusion during 1978-1985; persons seeking treatment for STDs. Clinicians should also consider local epidemiology.

HR4 = Consider for persons who have not received influenza vaccine or are vaccinated late; when the vaccine may be ineffective due to major antigenic changes in the virus; to supplement protection provided by vaccine in persons who are expected to have a poor antibody response; and for high-risk persons in whom the vaccine is contraindicated.

HR5 = Persons aged 75 years and older; or aged 70-74 with one or more additional risk factors including: use of certain psychoactive and cardiac medications (e.g., benzodiazepines, antihypertensives); use of >4 prescription medications; impaired cognition, strength, balance, or gait. Intensive individualized home-based multifactorial fall prevention intervention is recommended in settings where adequate resources are available to deliver such services.

HR6 = Although evidence is insufficient to recommend routine screening in elderly persons, clinicians should consider cholesterol screening on a case-by-case basis for persons ages 65-75 with additional risk factors (e.g., smoking, diabetes, or hypertension).

HR7 = Persons with a family or personal history of skin cancer, a large number of moles, atypical moles, poor tanning ability, or light skin, hair, and eye color.

~~**HR8** = Blood product recipients (including hemodialysis patients), men who have sex with men, injection drug users and their sex partners, persons with multiple recent sex partners, persons with other STDs~~

Immunization Guideline

~~(including HIV).~~

HR9 = Persons who exchange sex for money or drugs, and their sex partners; persons with other STDs (including HIV); and sexual contacts of persons with active syphilis. Clinicians should also consider local epidemiology.

HR10 = Persons who continue to inject drugs.

~~**HR11** = Healthy adults without a history of chickenpox or previous immunization. Consider serologic testing for presumed susceptible adults.~~

HR12 = A family history of breast or ovarian cancer that includes a relative with a known deleterious mutation in BRCA1 or BRCA2 genes; two first-degree relatives with breast cancer, one of whom received the diagnosis at age 50 years or younger; a combination of three or more first- or second degree relatives with breast cancer regardless of age at diagnosis; a combination of both breast and ovarian cancer among first- and second- degree relatives; a first-degree relative with bilateral breast cancer; a combination of two or more first- or second-degree relatives with ovarian cancer regardless of age at diagnosis; a first- or second-degree relative with both breast and ovarian cancer at any age; and a history of breast cancer in a male relative. For women of Ashkenazi Jewish heritage, an increased family history risk includes any first-degree relative (or two second degree relatives on the same side of the family) with breast or ovarian cancer.

Immunization Guideline

Pregnant Women**

Interventions Considered and Recommended for the Periodic Health Examination

Interventions for the General Population

First visit

Blood pressure
Hemoglobin/hematocrit
Hepatitis B surface antigen (HBsAg)
RPR/VDRL
Chlamydia screen (<25 yr)
Rubella serology or vaccination history
D(Rh) typing, antibody screen
Offer CVS (<13 wk)¹ or amniocentesis (15-18 wk)¹
(age>35 yr)
Offer hemoglobinopathy screening
Assess for problem or risk drinking
HIV screening

Follow-up visits

Blood pressure
Urine culture (12-16 wk)

Screening for gestational diabetes²
Offer amniocentesis (15-18 wk)¹ (age>35 yr)
Offer multiple marker testing¹ (15-18 wk)
Offer serum α -fetoprotein¹ (16-18 wk)

COUNSELING

Tobacco cessation; effects of passive smoking
Alcohol/other drug use
Nutrition, including adequate calcium intake Encourage
breastfeeding
Lap/shoulder belts
Infant safety car seats
STD prevention: avoid high-risk sexual behavior*; use
condoms*

CHEMOPROPHYLAXIS

Multivitamin with folic acid³

¹Women with access to counseling and follow-up services, reliable standardized laboratories, skilled high-resolution ultrasound, and, for those receiving serum marker testing, amniocentesis capabilities. ²Universal screening is recommended for areas (states, counties, or cities) with an increased prevalence of HIV infection among pregnant women. In low-prevalence areas, the choice between universal and targeted screening may depend on other considerations (see Ch. 28). ³Beginning at least 1 mo before conception and continuing through the first trimester..

*The ability of clinical counseling to influence this behavior is unproven.

**See tables for ages 11-24 and 25-64 for other preventive services recommended for women of these age groups.

Immunization Guideline

Pregnant Women (Cont'd)

Interventions for the High-Risk Population

POPULATION	POTENTIAL INTERVENTIONS
High-risk sexual behavior	(See detailed high-risk definitions) Screen for chlamydia (1st visit) (HR1), gonorrhea (1st visit) (HR2), HIV (1st visit) (HR3); HBsAg (3rd trimester) (HR4); RPR/VDRL (3rd trimester) (HR5)
Injection drug use	HBsAg (3rd trimester) (HR4); advice to reduce infection risk (HR6)
Unsensitized D-negative women	D(Rh) antibody testing (24-28 wk) (HR7)
Risk factors for Down syndrome	Offer CVS ₁ (1st trimester), amniocentesis ₁ (15-18 wk) (HR8)
Previous pregnancy with neural tube defect	Offer amniocentesis ₁ (15-18 wk), folic acid 4.0 mg ₃ (HR9)
High risk for child abuse	Targeted case management

High Risk Groups

HR1 = Women with history of STD or new or multiple sex partners. Clinicians should also consider local epidemiology. Chlamydia screen should be repeated in 3rd trimester if at continued risk.

HR2 = Women under age 25 with two or more sex partners in the last year, or whose sex partner has multiple sexual contacts; women who exchange sex for money or drugs; and women with a history of repeated episodes of gonorrhea. Clinicians should also consider local epidemiology. Gonorrhea screen should be repeated in the 3rd trimester if at continued risk.

HR4 = Women who are initially HBsAg negative who are at high risk due to injection drug use, suspected exposure to hepatitis B during pregnancy, multiple sex partners

HR5 = Women who exchange sex for money or drugs, women with other STDs (including HIV), and sexual contacts of persons with active syphilis. Clinicians should also consider local epidemiology

HR6 = Women who continue to inject drugs

HR7 = Unsensitized D-negative women

HR8 = Prior pregnancy affected by Down syndrome, advanced maternal age (>35 yr), known carriage of chromosome rearrangement

HR9 = Women with previous pregnancy affected by neural tube defect

DMAP Covered Immunizations

 Universal recommendation in the age group

 Recommendation for some individuals in the age group

	0 to 6 months	6 months to 8 months	8 months to 9 months	9 months to 1 year	1 year to 5 years	5 years to 9 years	9 years to 11 years	11 years to 19 years	19 years to 21 years	22 years to 27 years	27 years to 50 years	50 years to 60 years	60 years to 65 years	65 years and older
Hepatitis B (Hepatitis B or Twinrix)														
Rotavirus														
Diphtheria, Tetanus, and/or Pertussis (DTaP , DT , or Tdap/Td)														
H. influenzae type B														
Pneumococcal (PCV13 or PPSV23)														
Polio														
Influenza (LAIV or TIV)														
Measles, Mumps, and Rubella														
Varicella														
Hepatitis A (Hepatitis A or Twinrix)														
Meningococcal														
Human papillomavirus (for females)														
Human papillomavirus (for males)														
Zoster														

Click vaccine name for details found in Oregon Health Authority Immunization Program model standing orders. Additional immunization recommendations for recipients of hematopoietic stem cell transplants may be found [here](#).

Reflexes Issue Summary

Question: Should Guideline Note 37 be further clarified with intent about the definition of “abnormal reflexes?”

Question Source: John Sattenspiel, LIPA, OHP Managed Care Medical Directors

Issue: Guideline Note 37 defines neurologic impairment, and abnormal reflexes can be one of the criteria. Dr. Sattenspiel raises the concern that abnormal reflexes are quite subjective and possibly over-interpreted.

From Dr. Sattenspiel

This statement is from Disorders of the Nervous System – Reeves & Swenson and in my mind it is a reasonable description of reflex examination and grading:

Examination of myotatic ("deep tendon") reflexes

The muscle stretch (myotatic) reflex is a simple reflex, with the receptor neuron having direct connections to the muscle spindle apparatus in the muscle and with the alpha motor neurons in the central nervous system that send axons back to that muscle (Fig. 8-1). Normal muscle stretch reflexes result in contraction only of the muscle whose tendon is stretched and the agonist muscles (i.e., muscles that have the same action). There is also inhibition of antagonist muscles.

Reflexes are graded at the bedside in a semi-quantitative manner. The response levels of deep tendon reflexes are grade 0-4+, with 2+ being normal. The designation "0" signifies no response at all, even after reinforcement. Reinforcement requires a maximal isometric contraction of muscles of a remote part of the body, such as clenching the jaw, pushing the hands or feet together (depending on whether an upper or lower limb reflex is being tested), or locking the fingers of the two hands and pulling (termed the Jendrassik maneuver). This kind of maneuver probably amplifies reflexes by two mechanisms: by distracting the patient from voluntarily suppressing the reflex and by decreasing the amount of descending inhibition.

The designation 1+ means a sluggish, depressed or suppressed reflex, while the term trace means that a barely detectable response is elicited. Reflexes that are noticeably more brisk than usual are designated 3+, while 4+ means that the reflex is hyperactive and that there is clonus present. Clonus is a repetitive, usually rhythmic, and variably sustained reflex response elicited by manually stretching the tendon. This clonus may be sustained as long as the tendon is manually stretched or may stop after up to a few beats despite continued stretch of the tendon. In this case it is useful to note how many beats are present.

Reflexes Issue Summary

One sign of reflex hyperactivity is contraction of muscles that have different actions while eliciting a muscle stretch reflex (for example, contraction of thigh adductors when testing the patellar reflex or contraction of finger flexor muscles when testing the brachioradialis reflex). This has been termed "pathological spread of reflexes."

*Practice observing normal reflexes in patients and initially among students is an excellent way to determine the range of normalcy. **Almost any grade of reflex (outside of sustained clonus) can be normal.** Asymmetry of reflexes is a key for determining normalcy when extremes of response do not make the designation obvious. The patient's symptoms may facilitate the determination of which side is normal, i.e., the more active or the less active side. If this is a problem, the remainder of the neurologic examination and findings usually clarify the issue.*

Decreased reflexes should lead to suspicion that the reflex arc has been affected. This could be the sensory nerve fiber but may also be the spinal cord gray matter or the motor fiber. This motor fiber (the anterior horn cell and its motor axon coursing through the ventral root and peripheral nerve) is termed the "lower motor neuron" (LMN). LMN lesions result in decreased reflexes. The descending motor tracts from the cerebral cortex and brain stem are termed the "upper motor neurons" (UMN). Lesions of the UMNs result in increased reflexes at the spinal cord by decreasing tonic inhibition of the spinal segment.

Lesions of the cerebellum and basal ganglia in humans are not associated with consistent changes in the muscle stretch reflex. Classically, destruction of the major portion of the cerebellar hemispheres in humans is associated with pendular deep-tendon reflexes. The reflexes are poorly checked so that when testing the patellar reflex, for example, the leg may swing to-and-fro (like a pendulum). In normal individuals, the antagonist muscles (in this example, the hamstrings) would be expected to dampen the reflex response almost immediately. However, this is not a common sign of cerebellar disease and many other signs of cerebellar involvement are more reliable and diagnostic (see [Chapt. 10](#)). Basal ganglia disease (e.g., parkinsonism) usually is not associated with any predictable reflex change; most often the reflexes are normal.

Note particularly the second highlighted section. I would advocate for a statement that reflex status could be removed; or at least clarified to require absence of reflexes or markedly diminished reflexes to be considered as objective evidence that meets the guideline for coverage. What we often see is reflexes graded on an 5 point scale, reported as 4/5, and presented as sufficient to meet criteria as objective findings of impairment.

Current Prioritized List Status

GUIDELINE NOTE 37, DISORDERS OF SPINE WITH NEUROLOGIC IMPAIRMENT

Line: 400

Neurologic impairment or radiculopathy is defined as objective evidence of one or more of the following:

Reflexes Issue Summary

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

Otherwise, disorders of spine not meeting these criteria (e.g. pain alone) fall on Line 562 ACUTE AND CHRONIC DISORDERS OF SPINE WITHOUT NEUROLOGIC IMPAIRMENT

HERC Staff Recommendation

1. Option 1 - Modify Guideline Note 37 as follows:

GUIDELINE NOTE 37, DISORDERS OF SPINE WITH NEUROLOGIC IMPAIRMENT

Line: 400

Neurologic impairment or radiculopathy is defined as objective evidence of one or more of the following:

- A) Abnormal reflexes ([i.e. asymmetric, with markedly diminished or absent reflexes](#))
- B) Segmental muscle weakness
- C) Segmental sensory loss
- D) EMG or NCV evidence of nerve root impingement
- E) Cauda equina syndrome,
- F) Neurogenic bowel or bladder
- G) Long tract abnormalities

Otherwise, disorders of spine not meeting these criteria (e.g. pain alone) fall on Line 562 ACUTE AND CHRONIC DISORDERS OF SPINE WITHOUT NEUROLOGIC IMPAIRMENT

2. Option 2 - make no change