



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

January 17, 2019

8:00 AM - 1:00 PM

**Wilsonville Holiday Inn, Dogwood Room
25425 SW 95th Ave
Wilsonville, Oregon**

Section 1.0

Call to Order

AGENDA
VALUE-BASED BENEFITS SUBCOMMITTEE
1/17/2019

8:00am - 1:00pm

Wilsonville Holiday Inn, Dogwood Room
25425 SW 95th Ave, Wilsonville, Oregon

A working lunch will be served at approximately 12:00 PM

All times are approximate

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|--------------|--|-----------------|
| I. | Call to Order, Roll Call, Approval of Minutes – Kevin Olson | 8:00 AM |
| II. | Staff report – Ariel Smits, Cat Livingston, Darren Coffman A. Subcutaneous immunotherapy in the home | 8:05 AM |
| III. | Straightforward/Consent agenda – Ariel Smits, Cat Livingston A. Consent table B. Straightforward changes to the benign bone and joint condition guideline C. Prolonged preventive services codes | 8:10 AM |
| IV. | 2020 Biennial Review A. Chronic Pain Taskforce report A. Reprioritization of certain chronic pain conditions B. Hidradenitis suppurativa C. SI joint dysfunction prioritization | 8:15 AM |
| V. | Previous discussion items A. Human donor breast milk guideline update B. Diabetes prevention program guideline update | 10:45 AM |
| VI. | New discussion items A. Failure to thrive B. Procalcitonin C. Fecal calprotectin D. Pulmonary rehabilitation | 11:00 AM |
| VII. | Coverage guidances A. Newer interventions for GERD B. Temporary Percutaneous Mechanical Circulatory Support with Impella Devices | 11:45 AM |
| VIII. | Public comment | 12:55 PM |
| IX. | Adjournment – Kevin Olson | 1:00 PM |

**Value-based Benefits Subcommittee Recommendations Summary
For Presentation to:
Health Evidence Review Commission on November 8, 2018**

For specific coding recommendations and guideline wording, please see the text of the 11/8/2018 VbBS minutes.

RECOMMENDED CODE MOVEMENT (effective 1/1/2019 unless otherwise noted)

- Add the diagnosis codes used for latent tuberculosis infection to a covered line
- Add the procedure code for Yttrium-90 therapy to the covered liver cancer line with a new guideline
- Add the procedure codes for amniotic membrane transplant for eye conditions to three covered lines and removed from 3 other covered lines
- Add the 2019 CPT codes to various covered and uncovered lines on the Prioritized List with guideline note changes as needed to accommodate these codes
- Add the 2019 HCPCS codes to various covered and uncovered lines on the Prioritized List with changes to guidelines as required by placements
- Add the 2019 CDT codes to various covered and uncovered lines on the Prioritized List
- Add the procedure code for the iStent glaucoma surgery to a covered line with a new guideline

ITEMS CONSIDERED BUT NO RECOMMENDATIONS FOR CHANGES MADE

- No change was made to the non-coverage of pancreas only transplant
- No change was made to the non-coverage of non-invasive prenatal screening for average risk women

RECOMMENDED GUIDELINE CHANGES (effective 1/1/2019 unless otherwise noted)

- Modify the non-prenatal genetic testing guideline, and remove the hereditary cancer testing section to make into its own guideline
- Modify the prenatal genetic testing guideline
- Modify the guideline on human donor breast milk for high-risk infants

VALUE-BASED BENEFITS SUBCOMMITTEE
Clackamas Community College
Wilsonville Training Center, Rooms 111-112
Wilsonville, Oregon
November 8, 2018
8:30 AM – 1:30 PM

Members Present: Kevin Olson, MD, Chair; Susan Williams, MD (via phone); Mark Gibson; Holly Jo Hodges, MD; Vern Saboe, DC (via phone, left at 12:30); Gary Allen, DMD; Adriane Irwin, PharmD (via phone at 10:15, left at 1:30).

Members Absent: none

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

Also Attending: K. Renae Wentz, MD (Oregon Health Authority); Kevin Sasadeusz, MD (Providence interventional radiology); Ken Kolbech, MD (OHSU interventional radiology); Pippa Newell, MD (Providence hepatobiliary surgery, via phone); Devki Saraiya and Karen Heller (Myriad); Alice Austin (OR Assoc. of Behavior Analysis); Katy McDowell (Tonkin Torp).

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

The meeting was called to order at 8:30 am and roll was called. Minutes from the October 2018 VbBS meeting were reviewed and approved with the addition of a guideline note entry for CardioMEMS to guideline note 173 in the appendix of the minutes. **Approved 6-0, Irwin absent.**

Smits reviewed the two errata items. There was no discussion. Smits noted that the fusion for sacroiliac joint dysfunction discussion was tabled until January to allow the Washington HTA group to complete their evidence review.

Coffman noted that this was Williams last meeting, and she was thanked for her excellent service to the VbBS and HERC.

➤ **Topic: Straightforward/Consent Agenda**

Discussion: There was no discussion about the consent agenda item. The diabetes prevention program topic was discussed with the HCPCS code discussion later in the meeting (see topic below).

Recommended Actions:

- 1) Add ICD10 R76.11 (Nonspecific reaction to tuberculin skin test without active tuberculosis) and R76.12 (Nonspecific reaction to cell mediated immunity measurement of gamma interferon antigen response without active tuberculosis) to line 50 PULMONARY TUBERCULOSIS

MOTION: To approve the recommendation stated in the consent agenda. **CARRIES 6-0** (*Absent: Irwin*)

➤ **Topic: Yttrium 90 therapy for limited circumstances in hepatocellular carcinoma (HCC)**

Discussion: Smits reviewed the summary document and the staff proposed changes.

Expert testimony was heard from Kevin Sasadeusz, MD (Providence interventional radiology); Ken Kolbech, MD (OHSU interventional radiology); and Pippa Newell, MD (Providence hepatobiliary surgery, via phone).

Sasadeusz critiqued the SARAH trial. He noted that that trial used a different form of Y90 than what is used in the US. Another critique of the SARAH study was that the patient selection not what the OHSU and Providence oncology groups consider appropriate (for example, some had main portal vein thrombosis, which is a contraindication). Additionally, many patients had already had locoregional therapy and so this selected patients who were radiation resistant. Physicians in SARAH trial may also not have been experienced in use of Y90. Newell noted that a large percent of patients in SARAH did not receive the treatment they were randomized to receive. Kolbech noted that this trial, like many other Y90 trials, was industry driven.

Sasadeusz stated that in using Y90 at Providence, patients are reviewed by a multidisciplinary group to see if they are appropriate for Y90. The Providence group does the best to try to keep cost down for Y90. Kolbech showed the OHSU HCC treatment algorithm, which is very similar to the algorithm from Providence in the meeting materials.

There was a question about whether main portal vein thrombosis was different than unilateral portal vein thrombosis. It was explained that unilateral portal vein thrombosis involves only one branch of the portal vein and is not a contraindication to Y90, while main portal vein thrombosis is a contraindication. The VbBS group decided to add wording to the proposed guideline to clarify this distinction.

It was noted that liver transplant for liver cancer is on line 560 CANCER OF LIVER AND INTRAHEPATIC BILE DUCTS. Based on this, the VbBS group discussed taking out #1 as criteria in the proposed guideline (use of Y90 to keep a patient on the transplant list). It was further noted that cirrhosis is covered on line 307 for liver transplant, so most patients with HCC would be eligible for liver transplant as they also have cirrhosis. Newell requested consideration for reprioritization of line 560, which will be done as a possible future biennial review topic. She noted that such a review should wait until January 2019, as new guidelines are coming out for liver transplant recommendations in HCC.

Discussion then turned to the second proposed criteria (downsizing of patients who would be eligible for definitive treatment including liver transplant). Newell stated that the more common curative treatment offered to patients is ablation. Patients need to have their tumor downsized to less than 3 cm to be eligible for ablation or resection. Kolbech noted that OHSU is the only liver transplant provider in Oregon. It is a long, complex process to get on the liver transplant list. He did not advise keeping proposed criteria #1 (see above); but he felt proposed criteria #2 should be kept.

There was discussion that >90% of patients in Oregon are treated with Y90 by OHSU or Providence. Gibson asked if there was a registry of these patients to follow outcomes. Newell noted that a large,

multicenter registry trial was currently underway. Kolbech noted that OHSU has a database for all their Y90 patients and uses the data for internal quality review. There was discussion about whether low volume providers should be allowed to use Y90. The experts felt that it was appropriate if done on the recommendation of a multidisciplinary team. VbBS members decided to add wording requiring that patients need an evaluation by a multidisciplinary team or tumor board prior to coverage of Y90 therapy. Kolbech noted that non-OHSU/Providence providers can submit patients to the OHSU tumor board for reviewed if desired.

Recommended Actions:

- 1) Remove CPT 79440 (Radiopharmaceutical therapy, by intra-articular administration) from all current lines except
 - a. 201 CANCER OF BONES
 - b. 400 BENIGN CONDITIONS OF BONE AND JOINTS AT HIGH RISK FOR COMPLICATIONS
 - c. 556 BENIGN NEOPLASM OF BONE AND ARTICULAR CARTILAGE INCLUDING OSTEOID OSTEOMAS; BENIGN NEOPLASM OF CONNECTIVE AND OTHER SOFT TISSUE
- 2) Add Yttrium 90 therapy to line 315 CANCER OF LIVER
 - a. CPT 79445 (Radiopharmaceutical therapy, by intra-arterial particulate administration for use in treating primary hepatocellular carcinoma or colorectal cancer metastatic to the liver)
 - b. HCPCS C2616 (Brachytherapy source, non-stranded, yttrium-90, per source, for use in treating primary liver cancer or metastatic cancer to the liver)
 - c. HCPCS S2095 (Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres, for use in treating primary liver cancer or metastatic cancer to the liver)
- 3) Remove the entry regarding Yttrium 90 from line 500/GN172 as shown in Appendix A
- 4) Add a new guideline to line 315 CANCER OF LIVER as shown in Appendix B

MOTION: To recommend the code and guideline note changes as modified. CARRIES 6-0. (Absent: Irwin)

➤ **Topic: Pancreas only transplant**

Discussion: Livingston reviewed the summary document. Coffman highlighted that the question was about transplanting the pancreas earlier rather than waiting until renal failure had occurred. Members discussed that pancreas transplant is a major surgery and the study showing increased risk of renal failure associated with pancreas transplant alone is concerning. Members discussed that there was insufficient evidence to support benefit and there are significant harms. Olson said if pancreas transplant was a home run then it may be worth it, but the evidence does not show pancreas transplant alone is effective. Allen asked about Medicare coverage for pancreas transplant alone. Livingston said it was covered but clarified that there was insufficient evidence supporting improved outcomes for the patients identified in those coverage guidelines.

Recommended Actions:

- 1) Make no change to the noncoverage of pancreas transplant alone

➤ **Topic: Amniotic membrane transplant for ocular conditions**

Discussion: Smits reviewed the summary document. There was no discussion.

Recommended Actions:

- 1) Remove ocular amniotic membrane transplant CPT codes [65778 (Placement of amniotic membrane on the ocular surface; without sutures), 65779 (Placement of amniotic membrane on the ocular surface; single layer, sutured), 65780 (Ocular surface reconstruction; amniotic membrane transplantation, multiple layers)] from the following lines:
 - a. 56 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE
 - b. 159 TOXIC EPIDERMAL NECROLYSIS AND STAPHYLOCOCCAL SCALDED SKIN SYNDROME; STEVENS-JOHNSON SYNDROME; ERYTHEMA MULTIFORME MAJOR; ECZEMA HERPETICUM
 - c. 213 BULLOUS DERMATOSES OF THE SKIN
- 2) Add ocular amniotic membrane transplant CPT codes (same as above) to the following lines:
 - a. 113 CANCER OF EYE AND ORBIT
 - b. 470 KERATOCONJUNCTIVITIS
 - c. 493 ECTROPION AND BENIGN NEOPLASM OF EYE

MOTION: To recommend the code changes as presented. **CARRIES 6-0.** (*Absent: Irwin*)

➤ **Topic: 2019 CPT code review**

Discussion: Smits reviewed the multiple summary documents and spreadsheets comprising the 2019 CPT code review. There was no discussion regarding the proposed placements of the straightforward, applied behavior analysis (ABA), or psychology testing codes.

There was specific discussion about the following CPT codes:

- 1) 76391 (Magnetic resonance (eg, vibration) elastography)
 - a. Wentz suggested adding this code to line 500 with exception criteria rather than to line 199 CHRONIC HEPATITIS; VIRAL HEPATITIS as it is less cost effective than non-MR elastography. Hodges felt that it was better to follow the staff recommendation and place on line 199 and allow the CCOs to PA the test. Gingerich noted that MR elastography was added to the hepatitis C guideline for obese patients and other patients for whom the more cost-effective tests to not work, a decision that was based on expert testimony. The decision was to add to line 199. It was noted that the hepatitis C guideline would need revisions if the MR elastography code was added to line 500.

Alice Austin, Public Policy Chair of the Oregon Association of Behavior Analysis, testified in favor of the ABA code placements.

There was a question about whether the coverage guidance on molecular biomarkers should be updated based on the decisions regarding the new oncology CPT codes. Olson felt that things were moving to panels of genes for oncology. There is also the question about covering the genetic test or

the medications for treatment of a cancer found to have a genetic mutation not initially studied for that cancer. Gingerich noted that next generation sequencing has been tabled by HTAS as a topic.

Recommended Actions:

- 1) The 2019 CPT codes were placed as shown in Appendix C
- 2) Various guidelines were modified as shown in Appendix A

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

➤ **Topic: 2019 HCPCS code review**

Discussion: Smits reviewed the summary documents. There was no substantial discussion of any of the HCPCS code placement at the VBBS meeting.

Note: The placement of HCPCS G0069 (Professional services for the administration of subcutaneous immunotherapy for each infusion drug administration calendar day in the individual's home, each 15 minutes) was changed at the subsequent HERC meeting on November 8, 2018. The revised placement is shown in Appendix D with the revision required to Guideline Note 173 shown in Appendix A. The VBBS decision was to recommend placement on lines 9,124,223,313,531,550,559, 566. The revised decision was to place on line 660 due to a recent MED report showing that evidence did not support home administration of immunotherapy because of concerns for anaphylaxis. HERC staff was directed to obtain the MED report and bring to the January meeting if the staff recommendation would be placement other than on line 660. See the HERC minutes for details.

Recommended Actions:

- 1) 2019 HCPCS code placement as shown in Appendix D
- 2) Guideline 173 entries as shown in Appendix A

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

➤ **Topic: Oral Health Advisory Panel report**

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

Recommended Actions:

- 1) The 2019 CDT codes were placed as shown in Appendix E

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

➤ **Topic: Genetic Advisory Panel (GAP) report – 2019 CPT code placement**

Discussion: Smits reviewed the various summary documents comprising the GAP report. There was no discussion regarding the recommended placement of the 2019 genetic CPT codes other than CPT 81443.

CPT 81443 (expanded carrier screening) was discussed in detail. Hodges was concerned about coverage for partners. The partner only needs to be tested for the few genes mom is positive for. Smits noted that a few gene tests may be more expensive than the panel, so just testing the few genes found in mom's test might be more expensive.

There was general concern about how to interpret the results. The VBBS members felt that the interpretation would be difficult for most maternity care providers, and that patients should have genetic counseling with this test, which is a limited resource. There was discussion about unintended harm of too much genetic information being given to patients with an unclear idea of how to deal with this information. There was concern over interventions that might be done that might not be needed, or additional testing done that might not be needed. Medicaid is a vulnerable population and needs protections in place.

There was also concern about how to control the quality of what genes are in the panel, to ensure that all include genes recommended by ACOG guidelines.

There was discussion that if VBBS/HERC chose not to cover panel testing, then CCOs could still cover it if they chose to do so. There was also discussion that if VBBS/HERC adopted coverage, that providers would not have to order the test if they did not feel comfortable interpreting the results.

Public testimony:

Devki Saraiya, Myriad Labs, testified that current OHP coverage for carrier screening is by ethnicity-based screening. Ethnicity-based screening finds only 53% of patients at risk for having a child with a condition vs expanded carrier screening approaches. ACOG has guidelines on when tests are included, and labs offering this type of test are following ACOG guidelines. Ethnicity screening is difficult to determine when appropriate for a patient. Labs offer genetic counseling to help to determine when a partner needs to be tested. Variants of uncertain significance are not reported by Myriad in the carrier screening testing. CPT is specific for carrier screening, so if mom is not affected but is a carrier, then the partner then needs to be tested; if he is a carrier, then pregnancy has a 25% chance of being affected. This is about pregnancy/preconception decision making. This type of testing might lead to need for prenatal diagnostic testing. Myriad tries to make genetic counseling available to patients and/or providers to help with interpretation. Wentz: "How does the provider know what information was given to the patient by Myriad?" Surai: "We try to send documentation to the provider when the patient allows us to do so."

Olson noted that providers included in the current guideline know how to counsel folks and so are more comfortable with these tests. Hodges noted that this type of testing involved a long sequence: test mom, then need to test dad, then possibly test pregnancy. This sequence takes time, requires follow up. She expressed concern for timing of such testing during pregnancy (late gestation testing has few options for treatment). Hodges was also concerned about adequate shared decision making without genetic counseling. Smits asked whether this concern could be addressed with an entry in the prenatal genetic testing guideline about requiring genetic counseling.

Saraiya noted that OHP is already doing cystic fibrosis and spinal muscular atrophy testing for everyone. This expanded carrier testing adds more autosomal recessive genes that typically don't have a family history. She reported that there is a study on clinical utility showing that 37% of couples who tested positive for both being carriers went on to have prenatal diagnostic testing such as amniocentesis. Therefore, this information is being used for pregnancy decisions.

Hodges noted that her CCO initially had a large demand from providers for expanded carrier screening, but that she found no push back from providers once she explained the lack of coverage for such a test by her CCO. She noted the initial push back came from providers that are being told that this is standard of care.

Gibson noted that ACOG is not evidence-based much of the time. There was discussion that expanded carrier screening was not appropriate to be ordered for every pregnancy. The group struggled with how to put reasonable guidance on who should get this test. There was discussion of not covering expanded carrier screening until the OB community brings this to HERC with a request for coverage and explains who really needs the testing and what to do with the data. Irwin wanted to hear from providers who order this test. It was noted that Dr. Adler, an OB/Gyn, would be at the later HERC meeting and could give input.

The decision on expanded carrier screening was to put the CPT code on line 660 with a GN173 entry and leave prenatal guideline entries expressly stating this test is not covered. The HERC should revisit expanded carrier screening in the future to see if this testing should be covered with GN changes if brought forward by OB/maternity care community.

Recommended Actions:

- 1) The 2019 genetics CPT codes were placed as shown in Appendix C
- 2) GN173 was modified as shown in Appendix A

MOTION: To recommend the code and guideline note changes as modified. CARRIES 6-0. (Absent: Saboe)

➤ **Topic: Genetic Advisory Panel (GAP) report – Changes to the non-prenatal genetic testing guideline**

Discussion: Smits reviewed the various summary documents comprising the GAP report. There was minimal discussion about the changes to the non-prenatal genetic testing guideline, apart from clarification that the hereditary cancer testing section was being removed in order to create a separate guideline note.

The proposed new hereditary cancer guideline note focused on the suggested removal of the definition of “suitably trained” providers doing genetic counseling. Hodges noted that the CCO medical directors were opposed to this change. The medical directors felt that there was a need to define who was adequately trained. A provider who does not have the outlined qualifications but convinces a medical director that they are indeed adequately trained can be allowed to do genetic counseling at a CCO's discretion.

Public testimony was heard from Karen Haller from Myriad Genetics. She discussed that the issue of access to genetic counseling is real and is discussed at GAP every year. There is a lack of providers in Oregon and in the US in general. NCCN delineates criteria for testing in these hereditary cases. NCCN and USPSTF do not state that genetic counselors need to see every patient, and list other types of providers equipped to give this type of counseling. This information is being used more and more frequently in care—screening changes, treatment changes, etc. Providers cannot adequately manage patients without this information. Multiple specialty societies have stated that this type of counseling is within the scope of their specialty.

Hodges noted that this section of the new hereditary cancer guideline is about elective testing of asymptomatic patients. Such testing is not time sensitive and can wait for genetic counseling. Olson also expressed concern that variants of uncertain significance is important factor in this situation.

The decision was made to not delete the definition of “suitably trained.”

The next discussion centered on the proposed change regarding wording for panel testing for hereditary cancers. The group wanted only NCCN guidelines mentioned (not “or other expert” guidelines).

Recommended Actions:

- 1) Modifications to the non-prenatal genetic testing guideline as shown in Appendix A
- 2) Creation of a new hereditary cancer testing guideline as shown in Appendix B
 - a. *Note: strikethrough and underlined language in the new guideline note reflects modifications from the wording as it originally appeared in the non-prenatal genetic testing guideline.*

MOTION: To recommend the guideline note changes as modified. CARRIES 6-0. (Absent: Saboe)

➤ **Topic: Genetic Advisory Panel (GAP) report – Changes to the prenatal genetic testing guideline**

Discussion: Smits reviewed the various summary documents comprising the GAP report. There was minimal discussion of the proposed changes to the prenatal genetic testing guideline other than non-invasive prenatal screening.

Non-invasive prenatal screening (NIPS) discussion:

Devki Sariaya, Myriad, testified that all guidelines say that using NIPS in the general population is appropriate, including ACOG. BCBS TEC report was redone in 2018 and found sufficient evidence that NIPS used in a general risk population improved health outcomes. She noted that any screening test performs less well in low-risk population because prevalence of the conditions being screened for are lower in this population. NIPS provides a 100-fold lower false positive rate, reduces rates of amniocentesis or CVS and avoids the cost and complications of these procedures. Evidence supports that it is a superior test to serum tests. Requested that coverage be extended to average risk population.

The VBBS members felt that NIPS should be reserved for high-risk women. If ACOG comes out with a guideline expressly recommending this test for all-risk women, then this coverage can be revisited.

Recommended Actions:

- 1) Modify the prenatal genetic testing guideline as shown in Appendix A
- 2) Make no changes to the lack of coverage for low-risk women for non-invasive prenatal screening

MOTION: To recommend the guideline note changes as modified. CARRIES 5-0. (Absent: Saboe, Irwin)

➤ **Topic: iStent and cataract removal**

Discussion: Smits reviewed the summary document. There was no discussion.

Recommended Actions:

- 3) Add CPT 0191T (Insertion of anterior segment aqueous drainage device, without extraocular reservoir; internal approach, into the trabecular meshwork) to line 139 GLAUCOMA, OTHER THAN PRIMARY ANGLE-CLOSURE
- 4) Add a new guideline note to line 139 as shown in Appendix B

MOTION: To recommend the code and guideline note changes as presented. CARRIES 5-0. (Absent: Saboe, Irwin)

➤ **Topic: Human donor breast milk indications**

Discussion: Livingston reviewed the summary document and highlighted limitations of the evidence. Wentz discussed that recurrent necrotizing enterocolitis can occur and so ongoing donor breast milk is important, although this may be primarily in hospitalized infants. Livingston clarified that this guideline only applies to infants who have been discharged from the hospital and spoke about the rationale for the modified language which would require ongoing medical need for human donor breast milk.

Recommended Actions:

- 1) Revise the Guideline Note on Human Donor Breast Milk for High Risk Infants as shown in Appendix A.
- 2) Delay implementation until October 1, 2019 because a State Plan Amendment (SPA) is necessary. *[Note: After further review, staff found a SPA is not necessary and implementation can occur 1/1/19.]*

MOTION: To recommend the code and guideline note changes as presented. CARRIES 5-0. (Absent: Saboe, Irwin)

➤ **Public Comment:**

No additional public comment was received.

- **Issues for next meeting:**
 - HERC staff will obtain the MED report on home immunotherapy administration for the VBBS/HERC information

- **Next meeting:**

January 17, 2019, at a location TBD.

- **Adjournment:**

The meeting adjourned at 1:50 PM.

DRAFT

Appendix A

Revised Guideline Notes

DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE

- A) Genetic tests are covered as diagnostic, unless they are listed below in section FE1 as excluded or have other restrictions listed in this guideline. To be covered, initial screening (e.g. physical exam, medical history, family history, laboratory studies, imaging studies) must indicate that the chance of genetic abnormality is > 10% and results would do at least one of the following:
- 1) Change treatment,
 - 2) Change health monitoring,
 - 3) Provide prognosis, or
 - 4) Provide information needed for genetic counseling for patient; or patient's parents, siblings, or children
- B) Pretest and posttest genetic counseling is required for presymptomatic and predisposition genetic testing. Pretest and posttest genetic evaluation (which includes genetic counseling) is covered when provided by a suitable trained health professional with expertise and experience in genetics.
- 1) "Suitably trained" is defined as board certified or active candidate status from the American Board of Medical Genetics, American Board of Genetic Counseling, or Genetic Nursing Credentialing Commission.
- C) A more expensive genetic test (generally one with a wider scope or more detailed testing) is not covered if a cheaper (smaller scope) test is available and has, in this clinical context, a substantially similar sensitivity. For example, do not cover CFTR gene sequencing as the first test in a person of Northern European Caucasian ancestry because the gene panels are less expensive and provide substantially similar sensitivity in that context.
- ~~D) Related to genetic testing for patients with breast/ovarian and colon/endometrial cancer or other related cancers suspected to be hereditary, or patients at increased risk to due to family history.~~
- ~~1) Services are provided according to the Comprehensive Cancer Network Guidelines.~~
 - ~~a) Lynch syndrome (hereditary colorectal, endometrial and other cancers associated with Lynch syndrome) services (CPT 81288, 81292-81300, 81317-81319, 81435, 81436) and familial adenomatous polyposis (FAP) services (CPT 81201-81203) should be provided as defined by the NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Colorectal V1.2018 (7/12/18) V3.2017 (10/10/17). www.nccn.org.~~
 - ~~b) Breast and ovarian cancer syndrome genetic testing services (CPT 81162-81167, 81211-81217, 81212, 81215-81217) for women without a personal history of breast, ovarian and other associated cancers should be provided to high risk women as defined by the US Preventive Services Task Force or according to the NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast and ovarian. V2.2019 (7/30/18) V1.2018 (10/3/17). www.nccn.org.~~
 - ~~c) Breast and ovarian cancer syndrome genetic testing services (CPT 81162-81167, 81211-81217, 81212, 81215-81217) for women with a personal history of breast, ovarian, and other associated cancers and for men with breast cancer should be provided according to the NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Breast and Ovarian. V2.2019 (7/30/18) V1.2018 (10/3/17). www.nccn.org.~~
 - ~~d) PTEN (Cowden syndrome) services (CPT 81321-81323) should be provided as defined by the NCCN Clinical Practice Guidelines in Oncology. Colorectal Screening. V1.2018 (7/12/18) V3.2017 (10/10/17). www.nccn.org.~~

Appendix A Revised Guideline Notes

- ~~2) Genetic counseling should precede genetic testing for hereditary cancer whenever possible.~~
 - ~~a) Pre and post test genetic counseling should be covered when provided by a suitable trained health professional with expertise and experience in cancer genetics. Genetic counseling is recommended for cancer survivors when test results would affect cancer screening.~~
 - ~~i) "Suitably trained" is defined as board certified or active candidate status from the American Board of Medical Genetics, American Board of Genetic Counseling, or Genetic Nursing Credentialing Commission.~~
 - ~~b) If timely pre-test genetic counseling is not possible for time-sensitive cases, appropriate genetic testing accompanied by pre- and post-test informed consent and post-test disclosure performed by a board-certified physician with experience in cancer genetics should be covered.~~
 - ~~i) Post-test genetic counseling should be performed as soon as is practical.~~
- ~~3) If the mutation in the family is known, only the test for that mutation is covered. For example, if a mutation for BRCA 1 has been identified in a family, a single site mutation analysis for that mutation is covered (CPT 81215), while a full sequence BRCA 1 and 2 (CPT 81211 ~~81163~~) 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.~~
- ~~5) Hereditary breast cancer related disorders genomic sequence analysis panels (CPT 81432, 81433, 81479) are only included if the panel test~~
 - ~~a) Includes at least 5 genes that the NCCN Clinical Practice Guidelines in Oncology—Genetic/Familial High-Risk Assessment: Colorectal V1.2018 (7/12/18) V3.2017 (10/10/17). and/or NCCN Clinical Practice Guidelines in Oncology—Genetic/Familial High-Risk Assessment: Breast and Ovarian V2.2019 (7/30/18) V1.2018 (10/3/17) include(s) with specific guidance on clinical management; and,~~
 - ~~b) Includes no more than a reasonable number of genes (e.g. 40 genes total).~~
- D) Related to diagnostic evaluation of individuals with intellectual disability (defined as a full scale or verbal IQ < 70 in an individual > age 5), developmental delay (defined as a cognitive index < 70 on a standardized test appropriate for children < 5 years of age), Autism Spectrum Disorder, or multiple congenital anomalies:
 - 1) CPT 81228, Cytogenomic constitutional microarray analysis for copy number variants for chromosomal abnormalities: Cover for diagnostic evaluation of individuals with intellectual disability/developmental delay; multiple congenital anomalies; or, Autism Spectrum Disorder accompanied by at least one of the following: dysmorphic features including macro or microcephaly, congenital anomalies, or intellectual disability/developmental delay in addition to those required to diagnose Autism Spectrum Disorder.
 - 2) CPT 81229, Cytogenomic constitutional microarray analysis for copy number variants for chromosomal abnormalities; plus cytogenetic constitutional microarray analysis for single nucleotide polymorphism (SNP) variants for chromosomal abnormalities: Cover for diagnostic evaluation of individuals with intellectual disability/developmental delay; multiple congenital anomalies; or, Autism Spectrum Disorder accompanied by at least one of the following: dysmorphic features including macro or microcephaly, congenital anomalies, or intellectual disability/developmental delay in addition to those required to

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- diagnose Autism Spectrum Disorder; only if (a) consanguinity and recessive disease is suspected, or (b) uniparental disomy is suspected, or (c) another mechanism is suspected that is not detected by the copy number variant test alone.
- 3) CPT 81243, 81244, [81171](#), [81172](#), Fragile X genetic testing is covered for individuals with intellectual disability/developmental delay. Although the yield of Fragile X is 3.5-10%, this is included because of additional reproductive implications.
 - 4) A visit with the appropriate specialist (often genetics, developmental pediatrics, or child neurology), including physical exam, medical history, and family history is covered. Physical exam, medical history, and family history by the appropriate specialist, prior to any genetic testing is often the most cost-effective strategy and is encouraged.
- E) Related to other tests with specific CPT codes:
- 1) Certain genetic tests have not been found to have proven clinical benefit. These tests are listed in Guideline Note 173, INTERVENTIONS THAT HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS; UNPROVEN INTERVENTIONS
 - 2) The following tests are covered only if they meet the criteria in section A above AND the specified situations:
 - a) CPT 81205, BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, Maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X): Cover only when the newborn screening test is abnormal and serum amino acids are normal
 - b) Diagnostic testing for cystic fibrosis (CF)
 - i) CFTR, cystic fibrosis transmembrane conductance regulator tests. CPT 81220, 81222, 81223: For infants with a positive newborn screen for cystic fibrosis or who are symptomatic for cystic fibrosis, or for clients that have previously been diagnosed with cystic fibrosis but have not had genetic testing, CFTR gene analysis of a panel containing at least the mutations recommended by the American College of Medical Genetics* (CPT 81220) is covered. If two mutations are not identified, CFTR full gene sequencing (CPT 81223) is covered. If two mutations are still not identified, duplication/deletion testing (CPT 81222) is covered. These tests may be ordered as reflex testing on the same specimen.
 - c) Carrier testing for cystic fibrosis
 - i) CFTR gene analysis of a panel containing at least the mutations recommended by the American College of Medical Genetics* (CPT 81220) is covered once in a lifetime.
 - d) CPT 81224, CFTR (cystic fibrosis transmembrane conductance regulator) (eg. cystic fibrosis) gene analysis; intron 8 poly-T analysis (eg. male infertility): Covered only after genetic counseling.
 - e) CPT 81240. F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant: Factor 2 20210G>A testing should not be covered for adults with idiopathic venous thromboembolism; for asymptomatic family members of patients with venous thromboembolism and a Factor V Leiden or Prothrombin 20210G>A mutation; or for determining the etiology of recurrent fetal loss or placental abruption.

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- f) CPT 81241. F5 (coagulation Factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant: Factor V Leiden testing should not be covered for: adults with idiopathic venous thromboembolism; for asymptomatic family members of patients with venous thromboembolism and a Factor V Leiden or Prothrombin 20210G>A mutation; or for determining the etiology of recurrent fetal loss or placental abruption.
- g) CPT 81247. G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; common variant(s) (eg, A, A-) should only be covered
 - i) After G6PD enzyme activity testing is done and found to be normal; AND either
 - (a) There is an urgent clinical reason to know if a deficiency is present, e.g. in a case of acute hemolysis; OR
 - (b) In situations where the enzyme activity could be unreliable, e.g. female carrier with extreme Lyonization.
- h) CPT 81248. G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; known familial variant(s) is only covered when the information is required for genetic counseling.
- i) CPT 81249. G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; full gene sequence is only covered
 - i) after G6PD enzyme activity has been tested, and
 - ii) the requirements under CPT 81247 above have been met, and
 - iii) common variants (CPT 81247) have been tested for and not found.
- j) 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.
- k) CPT 81221, SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z): The alpha-1-antitrypsin protein level should be the first line test for a suspected diagnosis of AAT deficiency in symptomatic individuals with unexplained liver disease or obstructive lung disease that is not asthma or in a middle age individual with unexplained dyspnea. Genetic testing of the 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.
- l) [CPT 81329, Screening for spinal muscular atrophy: is covered once in a lifetime for preconception testing or testing of the male partner of a pregnant female carrier](#)
- m) CPT 81415-81416, exome testing: A genetic counseling/geneticist consultation is required prior to ordering test
- n) CPT 81430-81431, Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel: Testing for mutations in GJB2 and GJB6 need to be done first and be negative in non-syndromic patients prior to panel testing.
- o) CPT 81440, 81460, 81465, mitochondrial genome testing: A genetic counseling/geneticist or metabolic consultation is required prior to ordering test.
- p) CPT 81412 Ashkenazi Jewish carrier testing panel: panel testing is only covered when the panel would replace and would be similar or lower cost than individual gene testing including CF carrier testing.

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* American College of Medical Genetics Standards and Guidelines for Clinical Genetics Laboratories. 2008 Edition, Revised ~~3/2011~~ 7/2018 and found at <https://www.acmg.net/StaticContent/SGs/CFTR%20Mutation%20Testing.pdf>.
<http://www.acmg.net/PDFLibrary/Cystic-Fibrosis-Population-Based-Carrier-Screening-Standards.pdf>

DIAGNOSTIC GUIDELINE D2, IMPLANTABLE CARDIAC LOOP RECORDERS/SUBCUTANEOUS CARDIAC RHYTHM MONITORS

Use of an implantable cardiac loop recorder (ICLR)/subcutaneous cardiac rhythm monitor is a covered service only when the patient meets all of the following criteria:

- 1) The evaluation is for recurrent transient loss of consciousness (TLoC); and
- 2) A comprehensive evaluation including 30 days of noninvasive ambulatory cardiac monitoring did not demonstrate a cause of the TLoC; and
- 3) A cardiac arrhythmia is suspected to be the cause of the TLoC; and
- 4) There is a likely recurrence of the TLoC within the battery longevity of the device.

ICLRs and subcutaneous cardiac rhythm monitors are not a covered service for evaluation of cryptogenic stroke or any other indication.

DIAGNOSTIC GUIDELINE D6, BREAST CANCER SCREENING IN ABOVE-AVERAGE RISK WOMEN

Annual screening mammography and annual screening MRI without computer-aided detection (CAD) are covered only for women at above-average risk of breast cancer. This coverage, beginning at 30 years of age, includes women who have one or more of the following:

- Greater than 20% lifetime risk of breast cancer
- BRCA1 or BRCA2 gene mutation, or who have not been tested for BRCA but have a first-degree relative who is a BRCA carrier
- A personal history or a first-degree relative diagnosed with Bannayan-Riley-Ruvalcaba syndrome, Cowden syndrome, or Li-Fraumeni syndrome
- Other germline gene mutations known to confer a greater than 20% lifetime risk of breast cancer

For women with a history of high dose chest radiation (≥ 20 Gray) before the age of 30, annual screening MRI without computer-aided detection (CAD) and annual screening mammography are covered beginning 8 years after radiation exposure or at age 25, whichever is later.

For women with both a personal history and a family history of breast cancer, annual mammography, annual breast MRI without computer-aided detection (CAD) and annual breast ultrasound are covered.

For women with increased breast density, supplemental screening with breast ultrasound, MRI, or digital breast tomosynthesis is not covered.

Breast PET-CT scanning and breast-specific gamma imaging are not covered for breast cancer screening.

The development of this guideline note was informed by a HERC coverage guidance. See <https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx>.

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DIAGNOSTIC GUIDELINE D17, PRENATAL GENETIC TESTING

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

- A) Genetic counseling (CPT 96040, HPCPS S0265) for high risk women who have family history of inheritable disorder or carrier state, ultrasound abnormality, previous pregnancy with aneuploidy, or elevated risk of neural tube defect.
- B) Genetic counseling (CPT 96040, HPCPS S0265) prior to consideration of chorionic villus sampling (CVS), amniocentesis, microarray testing, Fragile X, and spinal muscular atrophy screening
- C) Validated questionnaire to assess genetic risk in all pregnant women
- D) Screening high risk ethnic groups for hemoglobinopathies (CPT 83020, 83021)
- E) Screening for aneuploidy with any of five screening strategies [first trimester (nuchal translucency, beta-HCG and PAPP-A), integrated, serum integrated, stepwise sequential, and contingency] (CPT 76813, 76814, 81508-81511, [81512](#), [82105](#), [82677](#))
- F) Cell free fetal DNA testing (CPT 81420, 81507) for evaluation of aneuploidy in women who have an elevated risk of a fetus with aneuploidy (maternal age >34, family history or elevated risk based on screening).
- G) Ultrasound for structural anomalies between 18 and 20 weeks gestation (CPT 76811, 76812)
- H) CVS or amniocentesis (CPT 59000, 59015, [76945](#), [76946](#), 82106, 88235, [88261-88264](#), 88267, 88269, 88280, [88283](#), 88285, [88289](#), [88291](#)) for a positive aneuploidy screen, maternal age >34, fetal structural anomalies, family history of inheritable chromosomal disorder or elevated risk of neural tube defect.
- I) Array CGH (CPT 81228, 81229) when major fetal congenital anomalies are apparent on imaging, or with normal imaging when array CGH would replace karyotyping performed with CVS or amniocentesis in #8 above.
- J) FISH testing (CPT 88271, [88272](#), [88274](#), 88275) only if karyotyping is not possible due a need for rapid turnaround for reasons of reproductive decision-making (i.e. at 22w4d gestation or beyond)
- K) Screening for Tay-Sachs carrier status (CPT 81255) in high risk populations. First step is hex A, and then additional DNA analysis in individuals with ambiguous Hex A test results, suspected variant form of TSD or suspected pseudodeficiency of Hex A
- L) Screening for cystic fibrosis carrier status once in a lifetime (CPT 81220-81224)
- M) Screening for fragile X status (CPT 81243, 81244, [81171](#), [81172](#)) in patients with a personal or family history of
 - a. fragile X tremor/ataxia syndrome
 - b. premature ovarian failure
 - c. unexplained early onset intellectual disability
 - d. fragile X intellectual disability
 - e. unexplained autism through the pregnant woman's maternal line
- N) Screening for spinal muscular atrophy (CPT ~~81401~~ [81329](#)) once in a lifetime
- O) Screening those with Ashkenazi Jewish heritage for Canavan disease (CPT 81200), familial dysautonomia (CPT 81260), and Tay-Sachs carrier status (CPT 81255). Ashkenazi Jewish carrier panel testing (CPT 81412) is covered if the panel would replace and would be of similar or lower cost than individual gene testing including CF carrier testing.
- P) Expanded carrier screening only for those genetic conditions identified above

The following genetic screening tests are not covered:

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- A) Serum triple screen
- B) Screening for thrombophilia in the general population or for recurrent pregnancy loss
- C) Expanded carrier screening which includes results for conditions not explicitly recommended for coverage

The development of this guideline note was informed by a HERC [coverage guidance](https://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <https://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

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

Line 199

Given that a fibrosis score of $\geq F2$ is the threshold for antiviral treatment of Hepatitis C, the following are included on this line:

Imaging tests:

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

Blood tests (only if imaging tests are unavailable):

- Enhanced Liver Fibrosis (ELF™)
- Fibrometer™
- FIBROSpect® II
- FibroSure® (FibroTest®) [or ActiTest®](#)

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

Imaging tests:

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

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

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

- Real time tissue elastography
- Hepascore (FibroScore)

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

The development of this guideline note was informed by a HERC [coverage guidance](https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx). See <https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx>.

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GUIDELINE NOTE 148, BIOMARKER TESTS OF CANCER TISSUE

Lines 157,184,191,230,263,271,329

The use of tissue of origin testing (e.g. CPT 81504) is included on Line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS.

For early stage breast cancer, the following breast cancer genome profile tests are included on Line 191 when the listed criteria are met. One test per primary breast cancer is covered when the patient is willing to use the test results in a shared decision-making process regarding adjuvant chemotherapy. Lymph nodes with micrometastases less than 2 mm in size are considered node negative.

- Oncotype DX Breast Recurrence Score (CPT 81519) for breast tumors that are estrogen receptor positive, HER2 negative, and either lymph node negative, or lymph node positive with 1-3 involved nodes.
- EndoPredict (using CPT 81599) and Prosigna (CPT 81520 or PLA 0008M) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative.
- MammaPrint (using CPT 81521 or HCPCS S3854) for breast tumors that are estrogen receptor or progesterone receptor positive, HER2 negative, lymph node negative, and only in those cases categorized as high clinical risk.

EndoPredict, Prosigna, and MammaPrint are not included on Line 191 for early stage breast cancer with involved axillary lymph nodes. Oncotype DX Breast Recurrence Score is not included on Line 191 for breast cancer involving four or more axillary lymph nodes or more extensive metastatic disease.

Oncotype DX Breast DCIS Score (CPT 81479) and Breast Cancer Index ([CPT 81518](#) ~~may use CPT 81479, 81599, 84999, S3854~~) are included on Line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS.

For melanoma, BRAF gene mutation testing (CPT 81210) is included on Line 230.

For lung cancer, epidermal growth factor receptor (EGFR) gene mutation testing (CPT 81235) is included on Line 263 only for non-small cell lung cancer. KRAS gene mutation testing (CPT 81275) is not included on this line.

For colorectal cancer, KRAS gene mutation testing (CPT 81275) is included on Line 157. BRAF (CPT 81210) and Oncotype DX are not included on this line. Microsatellite instability (MSI) is included on the Line 660.

For bladder cancer, Urovysion testing is included on Line 660.

For prostate cancer, Oncotype DX Genomic Prostate Score, Prolaris Score Assay, and Decipher Prostate RP are included on Line 660.

The development of this guideline note was informed by a HERC coverage guidance on [Biomarkers Tests of Cancer Tissue for Prognosis and Potential Response to Treatment](#); the prostate-related portion of that

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coverage guidance was superseded by a [Coverage Guidance on Gene Expression Profiling for Prostate Cancer](https://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <https://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

GUIDELINE NOTE 172, INTERVENTIONS WITH MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS FOR CERTAIN CONDITIONS

Line 500

The following interventions are prioritized on Line 500 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS:

| | | | |
|-------|--|---|------------------|
| 79445 | Radiopharmaceutical therapy, by intra-arterial particulate administration for use in treating primary hepatocellular carcinoma or colorectal cancer metastatic to the liver | Low-cost-effectiveness compared to equally effective but less-expensive standard chemotherapies; concern for possible harms compared to standard chemotherapy | <u>May, 2018</u> |
| C2616 | Brachytherapy source, non-stranded, yttrium-90, per source, for use in treating primary liver cancer or metastatic cancer to the liver | | |
| S2095 | Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres, for use in treating primary liver cancer or metastatic cancer to the liver | | |

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 660

The following Interventions are prioritized on Line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

| Procedure Code | Intervention Description | Rationale | Last Review |
|-----------------------|--|--|--------------------------------|
| C8937 | Computer aided detection of breast MRI | Insufficient evidence of effectiveness | November, 2018 |

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|---|---|--|--|
| C9751 | Bronchoscopy, rigid or flexible, transbronchial ablation of lesion(s) by microwave energy | Insufficient evidence of effectiveness | November, 2018 |
| C9754 C9755 | Percutaneous arteriovenous fistula formation | Insufficient evidence of benefit | November, 2018 |
| G0069 | Subcutaneous immunotherapy in the home | Insufficient evidence of effectiveness; evidence of harm | November, 2018 |
| 33274 33275 | Leadless cardiac pacemakers | Insufficient evidence of effectiveness; evidence of harm | November, 2018 |
| 33289, 93264 C2624, C9741 | CardioMEMS™ – Implantable wireless pulmonary artery pressure monitor for heart failure monitoring | Insufficient evidence of effectiveness | October, 2018 Coverage guidance |
| 53854 | Transurethral destruction of prostate tissue; by radiofrequency generated water vapor | Insufficient evidence of effectiveness | November, 2018 |
| 64635-64636 C9752 C9753 | Radiofrequency ablation of the lumbar and sacral spine | Insufficient evidence of benefit | November, 2014 Coverage Guidance Blog |
| 76978 76979 | Ultrasound, targeted dynamic microbubble sonographic contrast characterization (non-cardiac) | Insufficient evidence of effectiveness | November, 2018 |
| 81237 | EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, diffuse large B-cell lymphoma) gene analysis, common variant(s) (eg, codon 646) | Insufficient evidence of effectiveness | November, 2018 |
| 81306 | NUDT15 (nudix hydrolase 15) (eg, drug metabolism) gene analysis | Insufficient evidence of effectiveness | November, 2018 |
| 81320 | PLCG2 (phospholipase C gamma 2) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, R665W, S707F, L845F) | Insufficient evidence of effectiveness | November, 2018 |
| 81345 | TERT (telomerase reverse transcriptase) (eg, thyroid | Insufficient evidence of effectiveness | November, 2018 |

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| | | | |
|---|--|--|---|
| | carcinoma, glioblastoma multiforme) gene analysis, targeted sequence analysis (eg, promoter region) | | |
| 81443 | Expanded carrier screening | Insufficient evidence of effectiveness | November, 2018 |
| 81518 | Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 11 genes (7 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithms reported as percentage risk for metastatic recurrence and likelihood of benefit from extended endocrine therapy | Insufficient evidence of effectiveness | November, 2018 Coverage Guidance May, 2018 |
| Breast Cancer Gene Expression tests billed with nonspecific codes (e.g. 81479, 81599, 84999, S3854) | <ul style="list-style-type: none"> • Mammostrat • Oncotype DX Breast DCIS Score • Breast Cancer Index • IHC4 | Unproven intervention | May 2018 Coverage Guidance Blog |
| 83722 | Lipoprotein, direct measurement; small dense LDL cholesterol | Insufficient evidence of effectiveness | November, 2018 |
| 96116 96121 | Neurobehavioral status exam (clinical assessment of thinking, reasoning and judgment, eg, acquired knowledge, attention, language, memory, planning and problem solving, and visual spatial abilities) | | November, 2018 |

GUIDELINE NOTE XXX [HUMAN](#) DONOR BREAST MILK FOR HIGH RISK INFANTS

Line ~~2~~, 16, ~~18~~, 34, 88, 101

Donor breast milk ([T2101](#)) is included on these lines for infants up to 6 months of age (adjusted for gestational age) [who meet all of the following criteria](#):

- Low birth weight (<1500g) [OR with severe underlying gastrointestinal disease](#)

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- [Human donor milk was continued through neonatal hospital discharge for a clear medical indication](#)
- [Persistent outpatient medical need for human donor breast milk due to ongoing severe concerns with persistent diarrhea or malabsorption with improvement on breast milk compared to formula](#)
- When maternal breast milk is not available, appropriate or sufficient to meet the infant's needs, despite lactation support for the mother.

Donor human milk may only be obtained through a milk bank with appropriate quality and infection control standards.

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Appendix B New Guideline Notes

GUIDELINE NOTE 184 ANTERIOR SEGMENT AQUEOUS DRAINAGE DEVICE INSERTION

Line 139

Anterior segment aqueous drainage device (e.g. iStent©) insertion is only included on this line when done at the same time as cataract removal and when the two procedures are billed together as a bundled service.

GUIDELINE NOTE 185, YTTRIUM 90 THERAPY

Line 315

Yttrium 90 therapy is only included on this line for treatment of hepatocellular carcinoma (HCC) and only when recommended by a multidisciplinary tumor board or team in the following circumstances:

- 1) Downsizing tumors in patients who could become eligible for curative treatment (transplant, ablation, or resection), OR
- 2) Palliative treatment of incurable patients with unresectable or inoperable tumors that are not amenable to ablation therapy and
 - a. who have good liver function (Child-Pugh class A or B) and
 - b. good performance status (ECOG performance status 0-2), and
 - c. who have intermediate stage disease with tumors > 5 cm OR advanced stage HCC with unilateral (not main) portal vein tumor thrombus.

Note: strikethrough and underlined language for new diagnostic guideline D25 reflects modifications from the wording as it originally appeared in the non-prenatal genetic testing guideline

DIAGNOSTIC GUIDELINE D25, HEREDITARY CANCER GENETIC TESTING

- A) Related to genetic testing for patients with breast/ovarian and colon/endometrial cancer or other related cancers suspected to be hereditary, or patients at increased risk to due to family history.
 - 1) Services are provided according to the Comprehensive Cancer Network Guidelines.
 - a) Lynch syndrome (hereditary colorectal, endometrial and other cancers associated with Lynch syndrome) services (CPT 81288, 81292-81300, 81317-81319, 81435, 81436) and familial adenomatous polyposis (FAP) services (CPT 81201-81203) should be provided as defined by the NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Colorectal V1.2018 (7/12/18) ~~V3.2017 (10/10/17)~~. www.nccn.org.
 - b) Breast and ovarian cancer syndrome genetic testing services (CPT 81162-~~81167~~, ~~81211-81217~~ ~~81212~~, ~~81215-81217~~) for women patients without a personal history of breast, ovarian and other associated cancers should be provided to high risk women patients as defined by the US Preventive Services Task Force or according to the NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast and ovarian. V2.2019 (7/30/18) ~~V1.2018 (10/3/17)~~. www.nccn.org.
 - c) Breast and ovarian cancer syndrome genetic testing services (CPT 81162-~~81167~~, ~~81211-81217~~ ~~81212~~, ~~81215-81217~~) for women with a personal history of breast, ovarian, and or other associated cancers and for men with breast ~~cancer~~ or other associated cancers should be provided according to the NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Breast and Ovarian. V2.2019 (7/30/18) ~~V1.2018 (10/3/17)~~. www.nccn.org.

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- d) PTEN (Cowden syndrome) services (CPT 81321-81323) should be provided as defined by the NCCN Clinical Practice Guidelines in Oncology. [Genetic/Familial High-Risk Assessment: Breast and Ovarian. V2.2019 \(7/30/18\) or Genetic/Familial High-Risk Assessment: Colorectal Screening V1.2018 \(7/12/18\). V3.2017 \(10/10/17\).](#) www.nccn.org.
- 2) Genetic counseling should precede genetic testing for hereditary cancer whenever possible.
 - a) Pre and post-test genetic counseling should be covered when provided by a suitable trained health professional with expertise and experience in cancer genetics. Genetic counseling is recommended for cancer survivors when test results would affect cancer screening.
 - i) “Suitably trained” is defined as board certified or active candidate status from the American Board of Medical Genetics, American Board of Genetic Counseling, or Genetic Nursing Credentialing Commission.
 - b) If timely pre-test genetic counseling is not possible for time-sensitive cases, appropriate genetic testing accompanied by pre- and post- test informed consent and post-test disclosure performed by a board-certified physician with experience in cancer genetics should be covered.
 - i) Post-test genetic counseling should be performed as soon as is practical.
- 3) If the mutation in the family is known, only the test for that mutation is covered. For example, if a mutation for BRCA 1 has been identified in a family, a single site mutation analysis for that mutation is covered (CPT 81215), while a full sequence BRCA 1 and 2 (CPT ~~81214~~ [81163](#)) 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.
- 5) Hereditary breast cancer-related disorders genomic sequence analysis panels (CPT 81432, 81433, 81479) [are only included for patients meeting the criteria for hereditary cancer syndrome testing per NCCN guidelines](#)
 - ~~i) Includes at least 5 genes that the NCCN Clinical Practice Guidelines in Oncology—Genetic/Familial High-Risk Assessment: Colorectal V1.2018 (7/12/18) V3.2017 (10/10/17). and/or NCCN Clinical Practice Guidelines in Oncology—Genetic/Familial High-Risk Assessment: Breast and Ovarian V2.2019 (7/30/18) V1.2018 (10/3/17) include(s) with specific guidance on clinical management; and,~~
 - ~~ii) Includes no more than a reasonable number of genes (e.g. 40 genes total).~~

Appendix C
2019 CPT Codes

| code | long_code_description | Placement |
|-------|---|----------------------------|
| 10004 | Fine needle aspiration biopsy, without imaging guidance; each additional lesion (List separately in addition to code for primary procedure) | Diagnostic Procedures File |
| 10005 | Fine needle aspiration biopsy, including ultrasound guidance; first lesion | Diagnostic Procedures File |
| 10006 | Fine needle aspiration biopsy, including ultrasound guidance; each additional lesion (List separately in addition to code for primary procedure) | Diagnostic Procedures File |
| 10007 | Fine needle aspiration biopsy, including fluoroscopic guidance; first lesion | Diagnostic Procedures File |
| 10008 | Fine needle aspiration biopsy, including fluoroscopic guidance; each additional lesion (List separately in addition to code for primary procedure) | Diagnostic Procedures File |
| 10009 | Fine needle aspiration biopsy, including CT guidance; first lesion | Diagnostic Procedures File |
| 10010 | Fine needle aspiration biopsy, including CT guidance; each additional lesion (List separately in addition to code for primary procedure) | Diagnostic Procedures File |
| 10011 | Fine needle aspiration biopsy, including MR guidance; first lesion | Diagnostic Procedures File |
| 10012 | Fine needle aspiration biopsy, including MR guidance; each additional lesion (List separately in addition to code for primary procedure) | Diagnostic Procedures File |
| 11102 | Tangential biopsy of skin (eg, shave, scoop, saucerize, curette); single lesion | Diagnostic Procedures File |
| 11103 | Tangential biopsy of skin (eg, shave, scoop, saucerize, curette); each separate/additional lesion (List separately in addition to code for primary procedure) | Diagnostic Procedures File |
| 11104 | Punch biopsy of skin (including simple closure, when performed); single lesion | Diagnostic Procedures File |
| 11105 | Punch biopsy of skin (including simple closure, when performed); each separate/additional lesion (List separately in addition to code for primary procedure) | Diagnostic Procedures File |
| 11106 | Incisional biopsy of skin (eg, wedge) (including simple closure, when performed); single lesion | Diagnostic Procedures File |
| 11107 | Incisional biopsy of skin (eg, wedge) (including simple closure, when performed); each separate/additional lesion (List separately in addition to code for primary procedure) | Diagnostic Procedures File |
| 20932 | Allograft, includes templating, cutting, placement and internal fixation, when performed; osteoarticular, including articular surface and contiguous bone (List separately in addition to code for primary procedure) | Ancillary Procedures File |
| 20933 | Allograft, includes templating, cutting, placement and internal fixation, when performed; hemicortical intercalary, partial (ie, hemicylindrical) (List separately in addition to code for primary procedure) | Ancillary Procedures File |

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| 20934 | Allograft, includes templating, cutting, placement and internal fixation, when performed; intercalary, complete (ie, cylindrical) (List separately in addition to code for primary procedure) | Ancillary Procedures File |
| 27369 | Injection procedure for contrast knee arthrography or contrast enhanced CT/MRI knee arthrography | Diagnostic Procedures File |
| 33274 | Transcatheter insertion or replacement of permanent leadless pacemaker, right ventricular, including imaging guidance (eg, fluoroscopy, venous ultrasound, ventriculography, femoral venography) and device evaluation (eg, interrogation or programming), when performed | 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS |
| 33275 | Transcatheter removal of permanent leadless pacemaker, right ventricular | 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS |
| 33285 | Insertion, subcutaneous cardiac rhythm monitor, including programming | Diagnostic Procedures File |
| 33286 | Removal, subcutaneous cardiac rhythm monitor | 285 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT |
| 33289 | Transcatheter implantation of wireless pulmonary artery pressure sensor for long-term hemodynamic monitoring, including deployment and calibration of the sensor, right heart catheterization, selective pulmonary catheterization, radiological supervision and interpretation, and pulmonary artery angiography, when performed | 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS |

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| 33440 | Replacement, aortic valve; by translocation of autologous pulmonary valve and transventricular aortic annulus enlargement of the left ventricular outflow tract with valved conduit replacement of pulmonary valve (Ross-Konno procedure) | 82 MYOCARDITIS, PERICARDITIS, AND ENDOCARDITIS 106 CONGENITAL STENOSIS AND INSUFFICIENCY OF AORTIC VALVE 186 RHEUMATIC MULTIPLE VALVULAR DISEASE 189 CHRONIC ISCHEMIC HEART DISEASE 224 DISEASES AND DISORDERS OF AORTIC VALVE 285 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 366 ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS |
| 33866 | Aortic hemiarch graft including isolation and control of the arch vessels, beveled open distal aortic anastomosis extending under one or more of the arch vessels, and total circulatory arrest or isolated cerebral perfusion (List separately in addition to code for primary procedure) | 284 DISSECTING OR RUPTURED AORTIC ANEURYSM 325 NON-DISSECTING ANEURYSM WITHOUT RUPTURE |
| 36572 | Insertion of peripherally inserted central venous catheter (PICC), without subcutaneous port or pump, including all imaging guidance, image documentation, and all associated radiological supervision and interpretation required to perform the insertion; younger than 5 years of age | Ancillary Procedures File |
| 36573 | Insertion of peripherally inserted central venous catheter (PICC), without subcutaneous port or pump, including all imaging guidance, image documentation, and all associated radiological supervision and interpretation required to perform the insertion; age 5 years or older | Ancillary Procedures File |
| 38531 | Biopsy or excision of lymph node(s); open, inguinofemoral node(s) | Diagnostic Procedures File |
| 43762 | Replacement of gastrostomy tube, percutaneous, includes removal, when performed, without imaging or endoscopic guidance; not requiring revision of gastrostomy tract | Ancillary Procedures File |
| 43763 | Replacement of gastrostomy tube, percutaneous, includes removal, when performed, without imaging or endoscopic guidance; requiring revision of gastrostomy tract | Ancillary Procedures File |

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| 50436 | Dilation of existing tract, percutaneous, for an endourologic procedure including imaging guidance (eg, ultrasound and/or fluoroscopy) and all associated radiological supervision and interpretation, with postprocedure tube placement, when performed; | 180 URETERAL STRICTURE OR OBSTRUCTION; HYDRONEPHROSIS; HYDROURETER 231 URINARY FISTULA 352 URINARY SYSTEM CALCULUS |
| 50437 | Dilation of existing tract, percutaneous, for an endourologic procedure including imaging guidance (eg, ultrasound and/or fluoroscopy) and all associated radiological supervision and interpretation, with postprocedure tube placement, when performed; including new access into the renal collecting system | 180 URETERAL STRICTURE OR OBSTRUCTION; HYDRONEPHROSIS; HYDROURETER 231 URINARY FISTULA 352 URINARY SYSTEM CALCULUS |
| 53854 | Transurethral destruction of prostate tissue; by radiofrequency generated water vapor thermotherapy | 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS |
| 76391 | Magnetic resonance (eg, vibration) elastography | 199 CHRONIC HEPATITIS; VIRAL HEPATITIS |
| 76978 | Ultrasound, targeted dynamic microbubble sonographic contrast characterization (non-cardiac); initial lesion | 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS |
| 76979 | Ultrasound, targeted dynamic microbubble sonographic contrast characterization (non-cardiac); each additional lesion with separate injection (List separately in addition to code for primary procedure) | 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS |
| 76981 | Ultrasound, elastography; parenchyma (eg, organ) | 199 CHRONIC HEPATITIS; VIRAL HEPATITIS |
| 76982 | Ultrasound, elastography; first target lesion | 199 CHRONIC HEPATITIS; VIRAL HEPATITIS |
| 76983 | Ultrasound, elastography; each additional target lesion (List separately in addition to code for primary procedure) | 199 CHRONIC HEPATITIS; VIRAL HEPATITIS |
| 77046 | Magnetic resonance imaging, breast, without contrast material; unilateral | Diagnostic Procedures File |
| 77047 | Magnetic resonance imaging, breast, without contrast material; bilateral | Diagnostic Procedures File |
| 77048 | Magnetic resonance imaging, breast, without and with contrast material(s), including computer-aided detection (CAD real-time lesion detection, characterization and pharmacokinetic analysis), when performed; unilateral | Diagnostic Procedures File |

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|-------|--|----------------------------|
| 77049 | Magnetic resonance imaging, breast, without and with contrast material(s), including computer-aided detection (CAD real-time lesion detection, characterization and pharmacokinetic analysis), when performed; bilateral | Diagnostic Procedures File |
| 81163 | BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis | Diagnostic Procedures File |
| 81164 | BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements) | Diagnostic Procedures File |
| 81165 | BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis | Diagnostic Procedures File |
| 81166 | BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements) | Diagnostic Procedures File |
| 81167 | BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements) | Diagnostic Procedures File |
| 81171 | AFF2 (AF4/FMR2 family, member 2 [FMR2]) (eg, fragile X mental retardation 2 [FRAXE]) gene analysis; evaluation to detect abnormal (eg, expanded) alleles | Diagnostic Procedures File |
| 81172 | AFF2 (AF4/FMR2 family, member 2 [FMR2]) (eg, fragile X mental retardation 2 [FRAXE]) gene analysis; characterization of alleles (eg, expanded size and methylation status) | Diagnostic Procedures File |
| 81173 | AR (androgen receptor) (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; full gene sequence | Diagnostic Procedures File |
| 81174 | AR (androgen receptor) (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; known familial variant | Diagnostic Procedures File |
| 81177 | ATN1 (atrophin 1) (eg, dentatorubral-pallidoluysian atrophy) gene analysis, evaluation to detect abnormal (eg, expanded) alleles | Diagnostic Procedures File |
| 81178 | ATXN1 (ataxin 1) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles | Diagnostic Procedures File |
| 81179 | ATXN2 (ataxin 2) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles | Diagnostic Procedures File |
| 81180 | ATXN3 (ataxin 3) (eg, spinocerebellar ataxia, Machado-Joseph disease) gene analysis, evaluation to detect abnormal (eg, expanded) alleles | Diagnostic Procedures File |

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| 81181 | ATXN7 (ataxin 7) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles | Diagnostic Procedures File |
| 81182 | ATXN8OS (ATXN8 opposite strand [non-protein coding]) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles | Diagnostic Procedures File |
| 81183 | ATXN10 (ataxin 10) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles | Diagnostic Procedures File |
| 81184 | CACNA1A (calcium voltage-gated channel subunit alpha1 A) (eg, spinocerebellar ataxia) gene analysis; evaluation to detect abnormal (eg, expanded) alleles | Diagnostic Procedures File |
| 81185 | CACNA1A (calcium voltage-gated channel subunit alpha1 A) (eg, spinocerebellar ataxia) gene analysis; full gene sequence | Diagnostic Procedures File |
| 81186 | CACNA1A (calcium voltage-gated channel subunit alpha1 A) (eg, spinocerebellar ataxia) gene analysis; known familial variant | Diagnostic Procedures File |
| 81187 | CNBP (CCHC-type zinc finger nucleic acid binding protein) (eg, myotonic dystrophy type 2) gene analysis, evaluation to detect abnormal (eg, expanded) alleles | Diagnostic Procedures File |
| 81188 | CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; evaluation to detect abnormal (eg, expanded) alleles | Diagnostic Procedures File |
| 81189 | CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; full gene sequence | Diagnostic Procedures File |
| 81190 | CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; known familial variant(s) | Diagnostic Procedures File |
| 81204 | AR (androgen receptor) (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; characterization of alleles (eg, expanded size or methylation status) | Diagnostic Procedures File |
| 81233 | BTK (Bruton's tyrosine kinase) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, C481S, C481R, C481F) | 418 CHRONIC LEUKEMIAS WITH POOR PROGNOSIS |
| 81234 | DMPK (DM1 protein kinase) (eg, myotonic dystrophy type 1) gene analysis; evaluation to detect abnormal (expanded) alleles | Diagnostic Procedures File |
| 81236 | EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, myelodysplastic syndrome, myeloproliferative neoplasms) gene analysis, full gene sequence | Diagnostic Procedures File |

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| 81237 | EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, diffuse large B-cell lymphoma) gene analysis, common variant(s) (eg, codon 646) | 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS |
| 81239 | DMPK (DM1 protein kinase) (eg, myotonic dystrophy type 1) gene analysis; characterization of alleles (eg, expanded size) | Diagnostic Procedures File |
| 81271 | HTT (huntingtin) (eg, Huntington disease) gene analysis; evaluation to detect abnormal (eg, expanded) alleles | Diagnostic Procedures File |
| 81274 | HTT (huntingtin) (eg, Huntington disease) gene analysis; characterization of alleles (eg, expanded size) | Diagnostic Procedures File |
| 81284 | FXN (frataxin) (eg, Friedreich ataxia) gene analysis; evaluation to detect abnormal (expanded) alleles | Diagnostic Procedures File |
| 81285 | FXN (frataxin) (eg, Friedreich ataxia) gene analysis; characterization of alleles (eg, expanded size) | Diagnostic Procedures File |
| 81286 | FXN (frataxin) (eg, Friedreich ataxia) gene analysis; full gene sequence | Diagnostic Procedures File |
| 81289 | FXN (frataxin) (eg, Friedreich ataxia) gene analysis; known familial variant(s) | Diagnostic Procedures File |
| 81305 | MYD88 (myeloid differentiation primary response 88) (eg, Waldenstrom's macroglobulinemia, lymphoplasmacytic leukemia) gene analysis, p.Leu265Pro (L265P) variant | Diagnostic Procedures File |
| 81306 | NUDT15 (nudix hydrolase 15) (eg, drug metabolism) gene analysis, common variant(s) (eg, *2, *3, *4, *5, *6) | 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS |
| 81312 | PABPN1 (poly[A] binding protein nuclear 1) (eg, oculopharyngeal muscular dystrophy) gene analysis, evaluation to detect abnormal (eg, expanded) alleles | Diagnostic Procedures File |
| 81320 | PLCG2 (phospholipase C gamma 2) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, R665W, S707F, L845F) | 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS |
| 81329 | SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; dosage/deletion analysis (eg, carrier testing), includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed | Diagnostic Procedures File |

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|-------|---|--|
| 81333 | TGFBI (transforming growth factor beta-induced) (eg, corneal dystrophy) gene analysis, common variants (eg, R124H, R124C, R124L, R555W, R555Q) | Diagnostic Procedures File |
| 81336 | SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; full gene sequence | Diagnostic Procedures File |
| 81337 | SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; known familial sequence variant(s) | Diagnostic Procedures File |
| 81343 | PPP2R2B (protein phosphatase 2 regulatory subunit Bbeta) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles | Diagnostic Procedures File |
| 81344 | TBP (TATA box binding protein) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles | Diagnostic Procedures File |
| 81345 | TERT (telomerase reverse transcriptase) (eg, thyroid carcinoma, glioblastoma multiforme) gene analysis, targeted sequence analysis (eg, promoter region) | 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS |
| 81443 | Genetic testing for severe inherited conditions (eg, cystic fibrosis, Ashkenazi Jewish-associated disorders [eg, Bloom syndrome, Canavan disease, Fanconi anemia type C, mucopolipidosis type VI, Gaucher disease, Tay-Sachs disease], beta hemoglobinopathies, phenylketonuria, galactosemia), genomic sequence analysis panel, must include sequencing of at least 15 genes (eg, ACADM, ARSA, ASPA, ATP7B, BCKDHA, BCKDHB, BLM, CFTR, DHCR7, FANCC, G6PC, GAA, GALT, GBA, GBE1, HBB, HEXA, IKBKAP, MCOLN1, PAH) | 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS |
| 81518 | Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 11 genes (7 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithms reported as percentage risk for metastatic recurrence and likelihood of benefit from extended endocrine therapy | 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS |
| 81596 | Infectious disease, chronic hepatitis C virus (HCV) infection, six biochemical assays (ALT, A2-macroglobulin, apolipoprotein A-1, total bilirubin, GGT, and haptoglobin) utilizing serum, prognostic algorithm reported as scores for fibrosis and necroinflammatory activity in liver | 199 CHRONIC HEPATITIS; VIRAL HEPATITIS |
| 82642 | Dihydrotestosterone (DHT) | Diagnostic Procedures File |

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|-------|--|---|
| 83722 | Lipoprotein, direct measurement; small dense LDL cholesterol | 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS |
| 90689 | Influenza virus vaccine, quadrivalent (IIV4), inactivated, adjuvanted, preservative free, 0.25 mL dosage, for intramuscular use | 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS |
| 92273 | Electroretinography (ERG), with interpretation and report; full field (ie, ffERG, flash ERG, Ganzfeld ERG) | Diagnostic Procedures File |
| 92274 | Electroretinography (ERG), with interpretation and report; multifocal (mfERG) | Diagnostic Procedures File |
| 93264 | Remote monitoring of a wireless pulmonary artery pressure sensor for up to 30 days, including at least weekly downloads of pulmonary artery pressure recordings, interpretation(s), trend analysis, and report(s) by a physician or other qualified health care professional | 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS |
| 95836 | Electrocorticogram from an implanted brain neurostimulator pulse generator/transmitter, including recording, with interpretation and written report, up to 30 days | 174 GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY WITHOUT MENTION OF IMPAIRMENT OF CONSCIOUSNESS 250 PARKINSON'S DISEASE 285 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT |
| 95976 | Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with simple cranial nerve neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional | 174 GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY WITHOUT MENTION OF IMPAIRMENT OF CONSCIOUSNESS 250 PARKINSON'S DISEASE 285 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT |

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| 95977 | Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with complex cranial nerve neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional | 174 GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY WITHOUT MENTION OF IMPAIRMENT OF CONSCIOUSNESS 250 PARKINSON'S DISEASE 285 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT |
| 95983 | Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain neurostimulator pulse generator/transmitter programming, first 15 minutes face-to-face time with physician or other qualified health care professional | 174 GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY WITHOUT MENTION OF IMPAIRMENT OF CONSCIOUSNESS 250 PARKINSON'S DISEASE 285 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT |
| 95984 | Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain neurostimulator pulse generator/transmitter programming, each additional 15 minutes face-to-face time with physician or other qualified health care professional (List separately in addition to code for primary procedure) | 174 GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY WITHOUT MENTION OF IMPAIRMENT OF CONSCIOUSNESS 250 PARKINSON'S DISEASE 285 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT |
| 96112 | Developmental test administration (including assessment of fine and/or gross motor, language, cognitive level, social, memory and/or executive functions by standardized developmental instruments when performed), by physician or other qualified health care professional, with interpretation and report; first hour | Diagnostic Procedures File |

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|-------|---|--|
| 96113 | Developmental test administration (including assessment of fine and/or gross motor, language, cognitive level, social, memory and/or executive functions by standardized developmental instruments when performed), by physician or other qualified health care professional, with interpretation and report; each additional 30 minutes (List separately in addition to code for primary procedure) | Diagnostic Procedures File |
| 96121 | Neurobehavioral status exam (clinical assessment of thinking, reasoning and judgment, [eg, acquired knowledge, attention, language, memory, planning and problem solving, and visual spatial abilities]), by physician or other qualified health care professional, both face-to-face time with the patient and time interpreting test results and preparing the report; each additional hour (List separately in addition to code for primary procedure) | 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS |
| 96130 | Psychological testing evaluation services by physician or other qualified health care professional, including integration of patient data, interpretation of standardized test results and clinical data, clinical decision making, treatment planning and report, and interactive feedback to the patient, family member(s) or caregiver(s), when performed; first hour | Diagnostic Procedures File |
| 96131 | Psychological testing evaluation services by physician or other qualified health care professional, including integration of patient data, interpretation of standardized test results and clinical data, clinical decision making, treatment planning and report, and interactive feedback to the patient, family member(s) or caregiver(s), when performed; each additional hour (List separately in addition to code for primary procedure) | Diagnostic Procedures File |
| 96132 | Neuropsychological testing evaluation services by physician or other qualified health care professional, including integration of patient data, interpretation of standardized test results and clinical data, clinical decision making, treatment planning and report, and interactive feedback to the patient, family member(s) or caregiver(s), when performed; first hour | 92 SEVERE/MODERATE HEAD INJURY: HEMATOMA/EDEMA WITH PERSISTENT SYMPTOMS 173 POSTTRAUMATIC STRESS DISORDER 193 AUTISM SPECTRUM DISORDERS 202 CHRONIC ORGANIC MENTAL DISORDERS INCLUDING DEMENTIAS |

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|-------|--|--|
| 96133 | Neuropsychological testing evaluation services by physician or other qualified health care professional, including integration of patient data, interpretation of standardized test results and clinical data, clinical decision making, treatment planning and report, and interactive feedback to the patient, family member(s) or caregiver(s), when performed; each additional hour (List separately in addition to code for primary procedure) | 92 SEVERE/MODERATE HEAD INJURY: HEMATOMA/EDEMA WITH PERSISTENT SYMPTOMS 173 POSTTRAUMATIC STRESS DISORDER 193 AUTISM SPECTRUM DISORDERS 202 CHRONIC ORGANIC MENTAL DISORDERS INCLUDING DEMENTIAS |
| 96136 | Psychological or neuropsychological test administration and scoring by physician or other qualified health care professional, two or more tests, any method; first 30 minutes | Diagnostic Procedures File |
| 96137 | Psychological or neuropsychological test administration and scoring by physician or other qualified health care professional, two or more tests, any method; each additional 30 minutes (List separately in addition to code for primary procedure) | Diagnostic Procedures File |
| 96138 | Psychological or neuropsychological test administration and scoring by technician, two or more tests, any method; first 30 minutes | Diagnostic Procedures File |
| 96139 | Psychological or neuropsychological test administration and scoring by technician, two or more tests, any method; each additional 30 minutes (List separately in addition to code for primary procedure) | Diagnostic Procedures File |
| 96146 | Psychological or neuropsychological test administration, with single automated, standardized instrument via electronic platform, with automated result only | Diagnostic Procedures File |
| 97151 | Behavior identification assessment, administered by a physician or other qualified health care professional, each 15 minutes of the physician's or other qualified health care professional's time face-to-face with patient and/or guardian(s)/caregiver(s) administering assessments and discussing findings and recommendations, and non-face-to-face analyzing past data, scoring/interpreting the assessment, and preparing the report/treatment plan | 193 AUTISM SPECTRUM DISORDERS 436 STEREOTYPED MOVEMENT DISORDER WITH SELF-INJURIOUS BEHAVIOR DUE TO NEURODEVELOPMENTAL DISORDER. |
| 97152 | Behavior identification-supporting assessment, administered by one technician under the direction of a physician or other qualified health care professional, face-to-face with the patient, each 15 minutes | 193 AUTISM SPECTRUM DISORDERS 436 STEREOTYPED MOVEMENT DISORDER WITH SELF-INJURIOUS BEHAVIOR DUE TO NEURODEVELOPMENTAL DISORDER. |

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|-------|---|---|
| 97153 | Adaptive behavior treatment by protocol, administered by technician under the direction of a physician or other qualified health care professional, face-to-face with one patient, each 15 minutes | 193 AUTISM SPECTRUM DISORDERS 436 STEREOTYPED MOVEMENT DISORDER WITH SELF-INJURIOUS BEHAVIOR DUE TO NEURODEVELOPMENTAL DISORDER. |
| 97154 | Group adaptive behavior treatment by protocol, administered by technician under the direction of a physician or other qualified health care professional, face-to-face with two or more patients, each 15 minutes | 193 AUTISM SPECTRUM DISORDERS 436 STEREOTYPED MOVEMENT DISORDER WITH SELF-INJURIOUS BEHAVIOR DUE TO NEURODEVELOPMENTAL DISORDER. |
| 97155 | Adaptive behavior treatment with protocol modification, administered by physician or other qualified health care professional, which may include simultaneous direction of technician, face-to-face with one patient, each 15 minutes | 193 AUTISM SPECTRUM DISORDERS 436 STEREOTYPED MOVEMENT DISORDER WITH SELF-INJURIOUS BEHAVIOR DUE TO NEURODEVELOPMENTAL DISORDER. |
| 97156 | Family adaptive behavior treatment guidance, administered by physician or other qualified health care professional (with or without the patient present), face-to-face with guardian(s)/caregiver(s), each 15 minutes | 193 AUTISM SPECTRUM DISORDERS 436 STEREOTYPED MOVEMENT DISORDER WITH SELF-INJURIOUS BEHAVIOR DUE TO NEURODEVELOPMENTAL DISORDER. |
| 97157 | Multiple-family group adaptive behavior treatment guidance, administered by physician or other qualified health care professional (without the patient present), face-to-face with multiple sets of guardians/caregivers, each 15 minutes | 193 AUTISM SPECTRUM DISORDERS 436 STEREOTYPED MOVEMENT DISORDER WITH SELF-INJURIOUS BEHAVIOR DUE TO NEURODEVELOPMENTAL DISORDER. |
| 97158 | Group adaptive behavior treatment with protocol modification, administered by physician or other qualified health care professional, face-to-face with multiple patients, each 15 minutes | 193 AUTISM SPECTRUM DISORDERS 436 STEREOTYPED MOVEMENT DISORDER WITH SELF-INJURIOUS BEHAVIOR DUE TO NEURODEVELOPMENTAL DISORDER. |
| 99451 | Interprofessional telephone/Internet/electronic health record assessment and management service provided by a consultative physician, including a written report to the patient's treating/requesting physician or other qualified health care professional, 5 minutes or more of medical consultative time | All lines with E&M codes |
| 99452 | Interprofessional telephone/Internet/electronic health record referral service(s) provided by a treating/requesting physician or other qualified health care professional, 30 minutes | All lines with E&M codes |

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2019 CPT Codes

| code | long_code_description | Placement |
|-------|--|---------------------------|
| 99453 | Remote monitoring of physiologic parameter(s) (eg, weight, blood pressure, pulse oximetry, respiratory flow rate), initial; set-up and patient education on use of equipment | Ancillary Procedures File |
| 99454 | Remote monitoring of physiologic parameter(s) (eg, weight, blood pressure, pulse oximetry, respiratory flow rate), initial; device(s) supply with daily recording(s) or programmed alert(s) transmission, each 30 days | Ancillary Procedures File |
| 99457 | Remote physiologic monitoring treatment management services, 20 minutes or more of clinical staff/physician/other qualified health care professional time in a calendar month requiring interactive communication with the patient/caregiver during the month | Ancillary Procedures File |
| 99491 | Chronic care management services, provided personally by a physician or other qualified health care professional, at least 30 minutes of physician or other qualified health care professional time, per calendar month, with the following required elements: multiple (two or more) chronic conditions expected to last at least 12 months, or until the death of the patient; chronic conditions place the patient at significant risk of death, acute exacerbation/decompensation, or functional decline; comprehensive care plan established, implemented, revised, or monitored. | All lines with E&M codes |

Appendix D
2019 HCPCS Codes

| HCPCS | Description | Placement |
|-------|---|---|
| C1823 | Generator, neurostimulator (implantable), non-rechargeable, with transvenous sensing and stimulation leads | 174 GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY WITHOUT MENTION OF IMPAIRMENT OF CONSCIOUSNESS 250 GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY WITHOUT MENTION OF IMPAIRMENT OF CONSCIOUSNESS 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS 346 CONDITIONS OF THE BACK AND SPINE WITH URGENT SURGICAL INDICATIONS 361 SCOLIOSIS 440 TRIGEMINAL AND OTHER NERVE DISORDERS 527 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS |
| C8937 | Computer-aided detection, including computer algorithm analysis of breast mri image data for lesion detection/characterization, pharmacokinetic analysis, with further physician review for interpretation (list separately in addition to code for primary procedure) | 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS |
| C9751 | Bronchoscopy, rigid or flexible, transbronchial ablation of lesion(s) by microwave energy, including fluoroscopic guidance, when performed, with computed tomography acquisition(s) and 3-d rendering, computer-assisted, image-guided navigation, and endobronchial ultrasound (ebus) guided transtracheal and/or transbronchial sampling (eg, aspiration[s]/biopsy[ies]) and all mediastinal and/or hilar lymph node stations or structures and therapeutic intervention(s) | 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS |
| C9752 | Destruction of intraosseous basivertebral nerve, first two vertebral bodies, including imaging guidance (e.g., fluoroscopy), lumbar/sacrum | 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS |
| C9753 | Destruction of intraosseous basivertebral nerve, each additional vertebral body, including imaging guidance (e.g., fluoroscopy), lumbar/sacrum (list separately in addition to code for primary procedure) | 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS |

Appendix D
2019 HCPCS Codes

| HCPCS | Description | Placement |
|-------|---|--|
| C9754 | Creation of arteriovenous fistula, percutaneous; direct, any site, including all imaging and radiologic supervision and interpretation, when performed and secondary procedures to redirect blood flow (e.g., transluminal balloon angioplasty, coil embolization, when performed) | 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS |
| C9755 | Creation of arteriovenous fistula, percutaneous using magnetic-guided arterial and venous catheters and radiofrequency energy, including flow-directing procedures (e.g., vascular coil embolization with radiologic supervision and interpretation, when performed) and fistulogram(s), angiography, venography, and/or ultrasound, with radiologic supervision and interpretation, when performed | 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS |
| G0068 | Professional services for the administration of anti-infective, pain management, chelation, pulmonary hypertension, and/or inotropic infusion drug(s) for each infusion drug administration calendar day in the individual's home, each 15 minutes | All lines with E&M codes |
| G0069 | Professional services for the administration of subcutaneous immunotherapy for each infusion drug administration calendar day in the individual's home, each 15 minutes | 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS |
| G0070 | Professional services for the administration of chemotherapy for each infusion drug administration calendar day in the individual's home, each 15 minutes | All lines with "chemotherapy" in the treatment description line |
| G0071 | Payment for communication technology-based services for 5 minutes or more of a virtual (non-face-to-face) communication between an rural health clinic (rhc) or federally qualified health center (fqhc) practitioner and rhc or fqhc patient, or 5 minutes or more of remote evaluation of recorded video and/or images by an rhc or fqhc practitioner, occurring in lieu of an office visit; rhc or fqhc only | All lines with E&M codes |
| G0076 | Brief (20 minutes) care management home visit for a new patient. for use only in a medicare-approved cmmi model. (services must be furnished within a beneficiary's home, domiciliary, rest home, assisted living and/or nursing facility) | Ancillary List |
| G0077 | Limited (30 minutes) care management home visit for a new patient. for use only in a medicare-approved cmmi model. (services must be furnished within a beneficiary's home, domiciliary, rest home, assisted living and/or nursing facility) | Ancillary List |

Appendix D
2019 HCPCS Codes

| HCPCS | Description | Placement |
|-------|--|----------------|
| G0078 | Moderate (45 minutes) care management home visit for a new patient. for use only in a medicare-approved cmmi model. (services must be furnished within a beneficiary's home, domiciliary, rest home, assisted living and/or nursing facility) | Ancillary List |
| G0079 | Comprehensive (60 minutes) care management home visit for a new patient. for use only in a medicare-approved cmmi model. (services must be furnished within a beneficiary's home, domiciliary, rest home, assisted living and/or nursing facility) | Ancillary List |
| G0080 | Extensive (75 minutes) care management home visit for a new patient. for use only in a medicare-approved cmmi model. (services must be furnished within a beneficiary's home, domiciliary, rest home, assisted living and/or nursing facility) | Ancillary List |
| G0081 | Brief (20 minutes) care management home visit for an existing patient. for use only in a medicare-approved cmmi model. (services must be furnished within a beneficiary's home, domiciliary, rest home, assisted living and/or nursing facility) | Ancillary List |
| G0082 | Limited (30 minutes) care management home visit for an existing patient. for use only in a medicare-approved cmmi model. (services must be furnished within a beneficiary's home, domiciliary, rest home, assisted living and/or nursing facility) | Ancillary List |
| G0083 | Moderate (45 minutes) care management home visit for an existing patient. for use only in a medicare-approved cmmi model. (services must be furnished within a beneficiary's home, domiciliary, rest home, assisted living and/or nursing facility) | Ancillary List |
| G0084 | Comprehensive (60 minutes) care management home visit for an existing patient. for use only in a medicare-approved cmmi model. (services must be furnished within a beneficiary's home, domiciliary, rest home, assisted living and/or nursing facility) | Ancillary List |
| G0085 | Extensive (75 minutes) care management home visit for an existing patient. for use only in a medicare-approved cmmi model. (services must be furnished within a beneficiary's home, domiciliary, rest home, assisted living and/or nursing facility) | Ancillary List |

Appendix D
2019 HCPCS Codes

| HCPCS | Description | Placement |
|-------|--|--------------------------------|
| G0086 | Limited (30 minutes) care management home care plan oversight. for use only in a medicare-approved cmmi model. (services must be furnished within a beneficiary's home, domiciliary, rest home, assisted living and/or nursing facility) | Ancillary List |
| G0087 | Comprehensive (60 minutes) care management home care plan oversight. for use only in a medicare-approved cmmi model. (services must be furnished within a beneficiary's home, domiciliary, rest home, assisted living and/or nursing facility) | Ancillary List |
| G2000 | Blinded administration of convulsive therapy procedure, either electroconvulsive therapy (ect, current covered gold standard) or magnetic seizure therapy (mst, non-covered experimental therapy), performed in an approved ide-based clinical trial, per treatment session | Excluded List |
| G2010 | Remote evaluation of recorded video and/or images submitted by an established patient (e.g., store and forward), including interpretation with follow-up with the patient within 24 business hours, not originating from a related e/m service provided within the previous 7 days nor leading to an e/m service or procedure within the next 24 hours or soonest available appointment | All lines with E&M codes |
| G2011 | Alcohol and/or substance (other than tobacco) abuse structured assessment (e.g., audit, dast), and brief intervention, 5-14 minutes | All lines with G0396 and G0397 |
| G2012 | Brief communication technology-based service, e.g. virtual check-in, by a physician or other qualified health care professional who can report evaluation and management services, provided to an established patient, not originating from a related e/m service provided within the previous 7 days nor leading to an e/m service or procedure within the next 24 hours or soonest available appointment; 5-10 minutes of medical discussion | All lines with E&M codes |

Appendix D
2019 HCPCS Codes

| HCPCS | Description | Placement |
|-------|--|----------------|
| G9978 | Remote in-home visit for the evaluation and management of a new patient for use only in a medicare-approved bundled payments for care improvement advanced (bpci advanced) model episode of care, which requires these 3 key components: a problem focused history; a problem focused examination; and straightforward medical decision making, furnished in real time using interactive audio and video technology. counseling and coordination of care with other physicians, other qualified health care professionals or agencies are provided consistent with the nature of the problem(s) and the needs of the patient or the family or both. usually, the presenting problem(s) are self limited or minor. typically, 10 minutes are spent with the patient or family or both via real time, audio and video intercommunications technology | Ancillary List |
| G9979 | Remote in-home visit for the evaluation and management of a new patient for use only in a medicare-approved bundled payments for care improvement advanced (bpci advanced) model episode of care, which requires these 3 key components: an expanded problem focused history; an expanded problem focused examination; straightforward medical decision making, furnished in real time using interactive audio and video technology. counseling and coordination of care with other physicians, other qualified health care professionals or agencies are provided consistent with the nature of the problem(s) and the needs of the patient or the family or both. usually, the presenting problem(s) are of low to moderate severity. typically, 20 minutes are spent with the patient or family or both via real time, audio and video intercommunications technology | Ancillary List |

Appendix D
2019 HCPCS Codes

| HCPCS | Description | Placement |
|-------|--|----------------|
| G9980 | Remote in-home visit for the evaluation and management of a new patient for use only in a medicare-approved bundled payments for care improvement advanced (bpci advanced) model episode of care, which requires these 3 key components: a detailed history; a detailed examination; medical decision making of low complexity, furnished in real time using interactive audio and video technology. counseling and coordination of care with other physicians, other qualified health care professionals or agencies are provided consistent with the nature of the problem(s) and the needs of the patient or the family or both. usually, the presenting problem(s) are of moderate severity. typically, 30 minutes are spent with the patient or family or both via real time, audio and video intercommunications technology | Ancillary List |
| G9981 | Remote in-home visit for the evaluation and management of a new patient for use only in a medicare-approved bundled payments for care improvement advanced (bpci advanced) model episode of care, which requires these 3 key components: a comprehensive history; a comprehensive examination; medical decision making of moderate complexity, furnished in real time using interactive audio and video technology. counseling and coordination of care with other physicians, other qualified health care professionals or agencies are provided consistent with the nature of the problem(s) and the needs of the patient or the family or both. usually, the presenting problem(s) are of moderate to high severity. typically, 45 minutes are spent with the patient or family or both via real time, audio and video intercommunications technology | Ancillary List |

Appendix D
2019 HCPCS Codes

| HCPCS | Description | Placement |
|-------|---|----------------|
| G9982 | Remote in-home visit for the evaluation and management of a new patient for use only in a medicare-approved bundled payments for care improvement advanced (bpci advanced) model episode of care, which requires these 3 key components: a comprehensive history; a comprehensive examination; medical decision making of high complexity, furnished in real time using interactive audio and video technology. counseling and coordination of care with other physicians, other qualified health care professionals or agencies are provided consistent with the nature of the problem(s) and the needs of the patient or the family or both. usually, the presenting problem(s) are of moderate to high severity. typically, 60 minutes are spent with the patient or family or both via real time, audio and video intercommunications technology | Ancillary List |
| G9983 | Remote in-home visit for the evaluation and management of an established patient for use only in a medicare-approved bundled payments for care improvement advanced (bpci advanced) model episode of care, which requires at least 2 of the following 3 key components: a problem focused history; a problem focused examination; straightforward medical decision making, furnished in real time using interactive audio and video technology. counseling and coordination of care with other physicians, other qualified health care professionals or agencies are provided consistent with the nature of the problem(s) and the needs of the patient or the family or both. usually, the presenting problem(s) are self limited or minor. typically, 10 minutes are spent with the patient or family or both via real time, audio and video intercommunications technology | Ancillary List |

Appendix D
2019 HCPCS Codes

| HCPCS | Description | Placement |
|-------|---|----------------|
| G9984 | Remote in-home visit for the evaluation and management of an established patient for use only in a medicare-approved bundled payments for care improvement advanced (bpci advanced) model episode of care, which requires at least 2 of the following 3 key components: an expanded problem focused history; an expanded problem focused examination; medical decision making of low complexity, furnished in real time using interactive audio and video technology. counseling and coordination of care with other physicians, other qualified health care professionals or agencies are provided consistent with the nature of the problem(s) and the needs of the patient or the family or both. usually, the presenting problem(s) are of low to moderate severity. typically, 15 minutes are spent with the patient or family or both via real time, audio and video intercommunications technology | Ancillary List |
| G9985 | Remote in-home visit for the evaluation and management of an established patient for use only in a medicare-approved bundled payments for care improvement advanced (bpci advanced) model episode of care, which requires at least 2 of the following 3 key components: a detailed history; a detailed examination; medical decision making of moderate complexity, furnished in real time using interactive audio and video technology. counseling and coordination of care with other physicians, other qualified health care professionals or agencies are provided consistent with the nature of the problem(s) and the needs of the patient or the family or both. usually, the presenting problem(s) are of moderate to high severity. typically, 25 minutes are spent with the patient or family or both via real time, audio and video intercommunications technology | Ancillary List |

Appendix D
2019 HCPCS Codes

| HCPCS | Description | Placement |
|-------|---|----------------|
| G9986 | Remote in-home visit for the evaluation and management of an established patient for use only in a medicare-approved bundled payments for care improvement advanced (bpci advanced) model episode of care, which requires at least 2 of the following 3 key components: a comprehensive history; a comprehensive examination; medical decision making of high complexity, furnished in real time using interactive audio and video technology. counseling and coordination of care with other physicians, other qualified health care professionals or agencies are provided consistent with the nature of the problem(s) and the needs of the patient or the family or both. usually, the presenting problem(s) are of moderate to high severity. typically, 40 minutes are spent with the patient or family or both via real time, audio and video intercommunications technology | Ancillary List |
| G9987 | Bundled payments for care improvement advanced (bpci advanced) model home visit for patient assessment performed by clinical staff for an individual not considered homebound, including, but not necessarily limited to patient assessment of clinical status, safety/fall prevention, functional status/ambulation, medication reconciliation/management, compliance with orders/plan of care, performance of activities of daily living, and ensuring beneficiary connections to community and other services; for use only for a bpci advanced model episode of care; may not be billed for a 30-day period covered by a transitional care management code | Ancillary List |

Appendix E
2019 CDT Codes

| CDT Code | Code description | Proposed Placement |
|-----------------|--|---|
| D0412 | blood glucose level test – in-office using a glucose meter | Diagnostic Procedures File |
| D1516 | space maintainer – fixed – bilateral, maxillary | 53 PREVENTIVE DENTAL SERVICES |
| D1517 | space maintainer – fixed – bilateral, mandibular | 53 PREVENTIVE DENTAL SERVICES |
| D1526 | space maintainer – removable – bilateral, maxillary | 53 PREVENTIVE DENTAL SERVICES |
| D1527 | space maintainer – removable – bilateral, mandibular | 53 PREVENTIVE DENTAL SERVICES |
| D5282 | removable unilateral partial denture – one-piece cast metal (including clasps and teeth), maxillary | 588 DENTAL CONDITIONS (E.G., CARIES, FRACTURED TOOTH) |
| D5283 | removable unilateral partial denture – one-piece cast metal (including clasps and teeth), mandibular | 588 DENTAL CONDITIONS (E.G., CARIES, FRACTURED TOOTH) |
| D5876 | add metal substructure to acrylic full denture (per arch) | 451 DENTAL CONDITIONS (E.G., MISSING TEETH, PROSTHESIS FAILURE) |
| D9130 | temporomandibular joint dysfunction – non-invasive physical therapies | 547 TMJ DISORDER |
| D9613 | infiltration of sustained release therapeutic drug – single or multiple sites | Excluded File |
| D9944 | occlusal guard – hard appliance, full arch | 644 DENTAL CONDITIONS WHERE TREATMENT RESULTS IN MARGINAL IMPROVEMENT |
| D9945 | occlusal guard – soft appliance, full arch | 644 DENTAL CONDITIONS WHERE TREATMENT RESULTS IN MARGINAL IMPROVEMENT |

Appendix E
2019 CDT Codes

| CDT Code | Code description | Proposed Placement |
|-----------------|--|---|
| D9946 | occlusal guard – hard appliance, partial arch | 644 DENTAL CONDITIONS WHERE TREATMENT RESULTS IN MARGINAL IMPROVEMENT |
| D9961 | duplicate/copy patient's records | Excluded File |
| D9990 | certified translation or sign-language services – per visits | Ancillary Procedures File |

Section 2.0

Staff Report

Home Administration of Subcutaneous Immunotherapy

Issue: At the November 8, 2018 VBBS meeting, the VBBS voted to recommend that 2019 HCPCS code G0069 (Professional services for the administration of subcutaneous immunotherapy for each infusion drug administration calendar day in the individual's home, each 15 minutes) be placed on all the lines with immunotherapy (lines 9,124,223,313,531,550,559, 566). At the subsequent HERC meeting on November 8th, the HERC changed this placement to line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS. The HERC heard testimony from Val King, MD MPH that the Center for Evidence Based Policy had recently done a MED review on home immunotherapy and found that subcutaneous immunotherapy was not recommended for home administration due to concerns for anaphylaxis. HERC staff was directed to obtain the MED report and bring to the January meeting to ensure that this was indeed the correct placement of this code.

MED 2018 Allergy Immunotherapy for Rhinoconjunctivitis: Recommendations, Coding, and Billing Practices

- 1) Key findings:
 - a. Subcutaneous immunotherapy (SCIT) should occur in a medically supervised setting, not in the home
 - b. Sublingual immunotherapy (SLIT) can be used in the home if there were no adverse events after first administration under the medical supervision of a provider capable of managing anaphylaxis.
- 2) These findings were based on expert guidelines

HERC staff recommendation:

- 1) This is an informational item only. Staff concurs with the HERC placement of HCPCS G0069 (Professional services for the administration of subcutaneous immunotherapy for each infusion drug administration calendar day in the individual's home, each 15 minutes) on line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS with the following entry to GN173

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 660

The following Interventions are prioritized on Line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

| Procedure Code | Intervention Description | Rationale | Last Review |
|-----------------------|--|--|--------------------------------|
| G0069 | Subcutaneous immunotherapy in the home | Insufficient evidence of effectiveness; evidence of harm | November, 2018 |

Section 3.0
Consent Agenda-
Straightforward Items

Consent Agenda Issues—January 2019

| Code | Code Description | Line(s) Involved | Issue | Recommendation(s) |
|----------------------------------|---|---|--|---|
| 44320 | Colostomy or skin level cecostomy | 239 CANCER OF OVARY | Colostomy is found on several pelvic malignancy lines and may be required based on the type of resection surgery done. | Add 44320 to line 239 |
| 68110 68115 68130 68135 | Excision of lesion, conjunctiva; up to 1 cm Over 1 cm Excision of lesion, conjunctiva; with adjacent sclera Destruction of lesion, conjunctiva | 113 CANCER OF EYE AND ORBIT 310 CORNEAL OPACITY AND OTHER DISORDERS OF CORNEA | A CCO requested review of conjunctiva procedures. There are conjunctival lesion diagnoses on both lines 113 and 310. 68110, 68115 and 68130 are only on uncovered lines, and 68135 is missing from one line. | Add 68110-68130 to lines 113 and 310 Add 68135 to line 310 |
| 28111- 28114 | Ostectomy, metatarsal head | 359 DEFORMITY/CLOSED DISLOCATION OF JOINT AND RECURRENT JOINT DISLOCATIONS 540 DEFORMITIES OF FOOT | These CPT codes were part of a hearings case. They are used for bunion surgery. This placement has not been reviewed in 10+ years. The appropriate placement is line 540, on which they also appear. Bunion diagnosis codes appear only on line 540. | Remove 28111-28114 from line 359 |

Straightforward Correction of Benign Bone and Joint Tumor Guideline

Question: Should the benign bone and joint tumor guideline be updated to reflect correct CPT coding?

Question source: Holly Jo Hodges, CCO medical director; HERC staff

Issue: Several of the CPT codes in GN137 BENIGN BONE TUMORS are incorrect and do not reflect the entirety of the conditions appearing on this line. Additionally, the guideline title does not reflect the inclusion of benign joint tumors.

HERC staff recommendations:

- 1) Rename GN137 to reflect inclusion of benign joint tumors
- 2) Remove specific CPT codes in the guideline as shown below and simply have the guideline refer to all diagnoses on this line

GUIDELINE NOTE 137, BENIGN BONE AND JOINT TUMORS

Lines 400,556

Treatment of benign conditions of joints (~~ICD-10-CM D18.09 synovial hemangioma, D17.79 lipoma arborescens, D48.1 tenosynovial giant cell tumor, M67.8 synovial chondromatosis and M12.2 villonodular synovitis~~) are included on Line 400 for those conditions only when there are significant functional problems of the joint due to size, location, or progressiveness of the disease. Treatment of all other benign joint conditions are included on Line 556.

Treatment of benign tumors of bones (~~ICD-10-CM D16.00-D16.9, K09.0, K09.1, M27.1, M27.40, M27.49, M85.40-M85.69~~) are included on Line 400 for those neoplasms associated with pathologic fractures, at high risk of fracture, or which cause function problems including impeding joint function due to size, causing nerve compression, have malignant potential or are considered precancerous. Treatment of all other benign bone tumors are included on Line 556

Prolonged Preventive Services Codes

Question: Should the placement of the Prolonged Preventive Services Codes be modified?

Question source: Alison Little, PacificSource CCO

Issue:

There seem to be increases in use of prolonged preventive services codes by non-PCP providers (e.g. physical therapists and speech therapists), for unclear reasons. These 2 codes, G0513 and G0514, are currently on more than 600 lines on the Prioritized List. These codes were new in 2018 and were added to the same lines as other preventive codes. Preventive services codes in general are widely distributed across the list, and these new codes mirrored that wide distribution. However, they are somewhat vague and there is a concern that they are not being used appropriately with regard to evidence-based preventive services. If prolonged preventive services were being done, then submission of a preventive ICD-10 code would be appropriate, and the services rendered should be on Line 3.

Codes in Question

G0513

Prolonged preventive service(s) (beyond the typical service time of the primary procedure), in the office or other outpatient setting requiring direct patient contact beyond the usual service; first 30 minutes (list separately in addition to code for preventive service)

G0514

Prolonged preventive service(s) (beyond the typical service time of the primary procedure), in the office or other outpatient setting requiring direct patient contact beyond the usual service; each additional 30 minutes (list separately in addition to code G0513 for additional 30 minutes of preventive service)

HERC Staff Recommendations:

- 1) Remove G0513 and G0514 from all lines except for Line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS

Section 4.0

Biennial Review

**Value-based Benefits
Subcommittee:
Chronic Pain Task Force Proposal
and HERC Staff Suggested
Revisions**

January 17, 2019

Health
Oregon
Authority



Agenda

- CPTF background
- Additional information reviewed
 - CCO survey
 - Center for Evidence-based Policy report on opioid tapering
- Additional information requested after the December CPTF meeting
 - Evidence on treatment of fibromyalgia with opioids
 - Estimate of potential number of patients affected
- Revised proposal
- Public testimony

CCO Survey

- Concern for increased costs
 - Non-pharmacologic services
 - Pharmacologic treatments (Lyrica, etc.)
- The CCOs were mixed on whether they thought coverage for fibromyalgia and chronic pain would improve the health of their patients or simplify administration
- Nearly all responding CCOs were interested in incorporating Oregon opioid prescribing guidelines (acute and chronic)

Center for Evidence-based Policy

Opioid Tapering Report

- Overall level of evidence very low
- Findings suggested that pain, function, and quality of life might improve during and after opioid discontinuation or dose reduction
- Scant evidence on harms associated with tapering strategies
 - 1 study noted increase in suicidal ideation, some increase in suicidal behavior in a population tapered due to aberrant behaviors
 - Withdrawal symptoms reported
- Reason for discontinuation (patient-initiated vs. clinician-initiated) was not correlated with pain score trajectory

Treatment of Fibromyalgia with Opioids

- Current guideline on Prioritized List states that “Use of opioids should be avoided due to evidence of harm in this condition.”
- Pharmacy and Therapeutics Committee reviewed medications for fibromyalgia and did not find evidence of benefit with opioids including tramadol

Estimates of Number of Patients Affected: Non-opioid Treatments

- Number of patients possibly gaining coverage for non-opioid pharmacologic therapy and non-pharmacologic pain treatments
 - Between July and December 2017, about 60,000 people had a medical claim associated with one of the five diagnoses in the proposal
 - Many of these 60,000 patients could have new access to treatments based on this proposal
 - Some already have qualifying diagnoses (e.g. about a third of these patients have comorbid back pain)

Estimates of Number of Patients Affected: Opioid Treatment

- Number of patients possibly having current opioid prescriptions affected by the proposal
 - About 10 percent of this population had long term opioid prescriptions
 - Many of this 10% had other diagnoses or other clinical issues
 - Therefore, it is estimated that 600-1200 patients might need to have their opioid treatments re-evaluated by their providers
- Some patients with previously non-covered diagnoses may gain access to opioid treatment

Other Considerations Based on Public/Expert Input

- Individualization of treatment
- Focus on doctor-patient relationship
- Focus on payer guideline rather than practice guideline
- Removal of reference to “centralized pain syndrome”
 - Lack of accepted definition
- Consideration of impact of tapers on behavioral health

Revised Recommendations

- Create a new line for five chronic pain conditions including fibromyalgia for the 2020 Biennial Review

CONDITION: FIBROMYALGIA, CHRONIC PAIN SYNDROME AND RELATED CONDITIONS

TREATMENT: LIMITED PHYSICAL MODALITIES, COGNITIVE BEHAVIORAL THERAPY, MEDICAL THERAPY

Diagnoses:

- Chronic pain due to trauma
- Other chronic postprocedural pain
- Other chronic pain
- Chronic pain syndrome
- Fibromyalgia

Procedures:

- Standard outpatient codes
- Psychotherapy (for CBT/ACT)
- Physical therapy
- Occupational therapy
- Acupuncture
- Health and behavior assessment

Revised Recommendations

- Create a new line for five chronic pain conditions including fibromyalgia for the 2020 Biennial Review as shown below

CONDITION: FIBROMYALGIA, CHRONIC PAIN SYNDROME AND RELATED CONDITIONS

TREATMENT: LIMITED PHYSICAL MODALITIES, COGNITIVE BEHAVIORAL THERAPY, MEDICAL THERAPY

ICD-10: G89.21 (Chronic pain due to trauma), G89.28 (Other chronic postprocedural pain), G89.29 (Other chronic pain), G89.4 (Chronic pain syndrome), M79.7 (Fibromyalgia)

CPT: 90785, 90832-90840, 90853 (psychotherapy—for CBT and ACT), 96150-96155 (Health and behavior assessment and intervention), 97110-97124, 97140-97168, 97530, 97535 (PT/OT), 97810-97814 (acupuncture), 98966-98969, 99051, 99060, 99070, 99078, 99201-99215, 99281-99285, 99304-99337, 99340-99404, 99408-99449, 99487-99490, 99495, 99496, 99605-99607 (medical office visits, including ER and SNF)

HCPCS: G0157-G0160 (PT/OT assistant), G0396-G0397 (alcohol and substance abuse screening), G0463-G0467, G0469, G0470 (FQHC care), G0490, G0511-G0513 (RFQHC care), G0514 (prolonged office visit)

New Guideline with Staff Suggested Changes

GUIDELINE NOTE XXX TREATMENT OF FIBROMYALGIA, CHRONIC PAIN SYNDROME AND RELATED CONDITIONS

- *Line XXX*

Chronic pain syndrome (ICD-10 G89.4), chronic pain due to trauma (ICD-10 G89.21), other chronic postprocedural pain (ICD-10 G89.28), other chronic pain (ICD-10 G89.29), and fibromyalgia (ICD-10 M79.7) are included on line XXX when symptoms have been present for at least 3 months.

The following treatments are included on line XXX:

- Office evaluation, consultation and education.
 - Pain education, if done, should include but not be limited to sleep, nutrition, stress reduction/mood, exercise, and knowledge of pain as a biopsychosocial phenomenon. All providers seeing managing chronic pain patients should be trained in pain science (e.g., a contemporary understanding of the central and peripheral nervous system in chronic pain), motivational interviewing, culturally sensitive care, and trauma informed care. Care should be multidisciplinary and focus on active therapies.

Guideline continued

- Cognitive behavioral therapy (CBT). The necessity for CBT should be re-evaluated every 90 days and coverage will only be continued if there is documented evidence of decreasing depression or anxiety symptomatology, improved ability to work/function, increased self-efficacy, or other clinically significant, objective improvement.
- The following therapies, when available, may be provided: adaptive and restorative yoga, Tai Chi, mindfulness training, massage, supervised exercise therapy (land based and aquatic), intensive interdisciplinary rehabilitation. HCPCS S9451 is only included on Line XXX for the provision of yoga or supervised exercise therapy.

Guideline continued

- A total of 30 visits per year of any combination of the following therapies when available and medically appropriate. These therapies are only included on these lines if provided by a provider licensed to provide the therapy and when there is documentation of measurable clinically significant progress toward the therapy plan of care goals and objectives using evidence-based objective tools. Once the pre-determined goals of care have been achieved, an additional two visits may be authorized for maintenance therapy to maintain these improvements. These 30 visits count toward the visit totals in GUIDELINE NOTE 56 NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE if the patient has comorbid back or spine conditions.
- Rehabilitative therapy (physical and/or occupational therapy), if provided according to Guideline Note 6 REHABILITATIVE AND HABILITATIVE THERAPIES. Rehabilitation services provided under this guideline also count towards visit totals in Guideline Note 6. CPT 97124 is included in this category.
- Acupuncture

Guideline continued

- Non-opioid medications are only included on line XXX if all of the following apply:
 - ~~The medication is FDA approved or supported by compendia for treatment of chronic, non-neuropathic pain.~~
 - The patient is also being treated with active therapy (e.g., physical therapy, CBT) or is continuing maintenance of self-management strategies learned from such therapy.
 - The benefit of non-opioid medication is re-evaluated at least every 90 days and medications are only continued if there is documented evidence of initial improvement of function of at least fifteen percent as compared to baseline based on a validated tool (e.g., Pain average, interference with Enjoyment of life, and interference with General activity” (PEG) Assessment Scale, Oswestry, Oswestry, SF-MPQ, MSPQ), and function is maintained thereafter. Less frequent monitoring may be appropriate for certain medications after safety and efficacy are established.

Guideline continued

Opioids for chronic pain syndrome (~~when not representing centralized pain syndrome~~), chronic pain due to trauma, other chronic postprocedural pain, and other chronic pain

- Chronic opioids (>90 days) are only covered for chronic pain syndrome (ICD-10 G89.4; ~~when not representing centralized pain syndrome~~), chronic pain due to trauma (ICD-10 G89.21), other chronic postprocedural pain (ICD-10 G89.28), and other chronic pain (ICD-10 G89.29) when all of the following are met:
 - In alignment with the Oregon Opioid Prescribing Guideline (2017-2018 version) <https://www.oregon.gov/oha/PH/PREVENTIONWELLNESS/SUBSTANCEUSE/OPIOIDS/Documents/taskforce/oregon-opioid-prescribing-guidelines.pdf>
 - Appropriate risk assessment has been performed (e.g., Opioid Risk Assessment Tool)
 - PDMP checked at least annually and shows no aberrant behavior
 - No concurrent prescribing of benzodiazepines without extenuating circumstances
 - Urine drug testing is performed at least once per year and is appropriate
 - No illicit drug use or active substance use disorder (excluding tobacco)

Guideline continued

- ~~○ MED < 50, or between 50 and 90 with extenuating circumstances [MED=morphine equivalent daily dose]. For patients at or above 50 MED, every attempt should be made to taper according to the taper guidelines (ideally to MED <50). Careful reassessment of the evidence of individual benefits and risks should be undertaken for dosages > 50 MED. Dosages >90 MED should be avoided or carefully justified.~~
- Initial functional improvement has been documented of at least 30%, and function is maintained throughout the prescribing period
- Comorbid mental health disorders are appropriately addressed
- No additional opioids are prescribed for flares of the chronic pain condition, although opioids may be prescribed separately for other acute injuries or surgeries as clinically appropriate
- Prescriber has updated opioid prescribing CME and ideally has completed the Oregon Pain Management Commission (OPMC) pain module
- Patient and provider have assessed the relative risks and benefits of therapy and agree benefits outweigh risks, and have completed a material risk notice <https://www.oregon.gov/omb/OMBForms1/material-risk-notice.pdf>
- The patient be prescribed the patient pain education module through OPMC when it becomes available

Guideline continued

Opioid tapering for fibromyalgia and ~~other chronic pain conditions on this line~~ patients failing to meet the opioid prescribing criteria above:

Opioids are not intended for inclusion on this line for the following conditions/situations due to the evidence for harm:

- fibromyalgia
- ~~centralized pain syndrome (sometimes coded as chronic pain syndrome, ICD-10 G89.4)~~
- patients who fail to meet the guideline requirements regarding opioids above who have chronic pain syndrome (~~when not representing centralized pain syndrome~~), chronic pain due to trauma, other chronic postprocedural pain, and other chronic pain conditions included on this line
-

Guideline continued

- If a patient is already receiving chronic opioid therapy for these conditions/situations, then tapering is indicated. Opioid tapering should be done on an individualized basis which includes a taper goal of zero. Tapering should be unidirectional with a shared goal set by the patient and provider, generally with a 5-10% decrease monthly, and can be paused or slowed if the prescriber believes this is medically appropriate based on the patient's overall status. Taper plans should include nonpharmacological treatment strategies for managing the patient's pain. During the taper, behavioral health conditions need to be regularly assessed and appropriately managed. In some situations (e.g., in the setting of active substance use disorder, history of opioid overdose, aberrant behavior), more rapid tapering or transition to medication assisted treatment may be appropriate and should be directed by the prescribing provider. If a patient has developed opioid use disorder, treatment is included on Line 4 SUBSTANCE USE DISORDER.

Line Scoring

- Line XXX FIBROMYALGIA, CHRONIC PAIN SYNDROME AND RELATED CONDITIONS
- Category: 7
- HL: 4
- Suffering: 3
- Population effects: 0
- Vulnerable population: 0
- Tertiary prevention: 2
- Effectiveness: 2
- Need for service: 0.8
- Net cost: 2
- Score: 288
- Approximate line placement: 443

Line 528 Revision

Line: 528

Condition: ~~FIBROMYALGIA, CHRONIC FATIGUE SYNDROME, AND RELATED DISORDERS~~ (See Guideline Notes 64,65,135)

Treatment: MEDICAL THERAPY

ICD-10: ~~G89.21, G89.28- G89.29, G89.4, M79.7, R53.82~~

CPT: 90785, 90832-90840, 90846-90853, 93792, 93793, 98966-98969, 99051, 99060, 99070, 99078, 99201-99215, 99281-99285, 99341-99378, 99381-99404, 99408-99449, 99487-99490, 99495-99498, 99605-99607

HCPCS: G0248-G0250, G0396, G0397, G0463-G0467, G0490, G0511, G0513, G0514

Other Proposed Changes

- Back conditions guideline note edits (GN 56)
 - Wording changes to tie into new chronic pain line/guideline
 - Deletion of obsolete table
- Opioids for back condition guideline note edits (GN 60)
 - Removes “flare” as indication for short term opioids
 - Tapering section revised to exactly match the section in the new chronic pain line guideline, with staff suggested edits
 - See wording on next slide
- Acupuncture guideline note edit (GN 92)
 - Adds entry for new line
- Delete fibromyalgia guideline note (GN 135)

Opioids for Back Conditions Guideline: Taper Paragraph

Transitional coverage for patients on long-term opioid therapy as of July 1, 2016:

For patients ~~on covered chronic~~ receiving long-term opioid therapy (>90 days) for conditions of the back and spine as of July 1, 2016, opioid medication is included on these lines only from July 1, 2016 to December 31, 2016. During the period from January 1, 2017 to December 31, 2017, continued coverage of opioid medications requires an individual treatment plan which includes a taper plan developed by January 1, 2017 which includes a taper with an end to opioid therapy no later than January 1, 2018.

Opioid tapering should be done on an individualized basis and include a taper goal to zero. Tapering should be unidirectional with a shared goal set by the patient and provider, generally with a 5-10% decrease monthly and can be paused or slowed if the prescriber believes this is medically appropriate based on the patient's overall status.

Taper plans ~~must~~ should include nonpharmacological treatment strategies for managing the patient's pain based on Guideline Note 56 NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE. During the taper, behavioral health conditions need to be regularly assessed and appropriately managed.

Opioids for Back Conditions Guideline: Taper Paragraph Revisions Continued

In some situations (e.g., in the setting of active substance use disorder, history of opioid overdose, aberrant behavior), more rapid tapering or transition to medication assisted treatment may be appropriate and should be directed by the prescribing provider. If a patient has developed dependence and/or addiction related to their opioids opioid use disorder, treatment is available included on Line 4 SUBSTANCE USE DISORDER.

Discussion

Next Steps

- VbBS action
 - January 2019 or March 2019
- HERC action on VbBS recommendations
 - March 2019
- Any approved changes will take effect January 1, 2020

**Chronic Pain Task Force
Proposal for Review by VbBS
January 2019**

Since the August VbBS meeting, the Chronic Pain Taskforce met twice. At its December meeting, it completed a revised proposal to create a new line for a limited number of chronic pain conditions (see [September CPTF Minutes](#), [December CPTF Minutes](#)). This revised proposal takes into several sources of new information, evidence and perspectives:

- extensive public testimony
- conversations with the pharmacy directors on what types of medication controls are implementable
- discussions with partners in public health and experts in Oregon on best practices for opioid prescribing
- a Pharmacy and Therapeutics Committee report on effective pharmacologic treatments for fibromyalgia
- feedback from CCOs on possible coverage changes
- the new CEBP MED report on opioid tapering

The key issues and discussion items are summarized below, followed by a description of other changes introduced by staff since the December CPTF meeting.

CCO survey take home points

- 1) For the back line changes:
 - a. Most CCOs answering the survey are implementing all or most of the back line guideline and providing new back/neck pain services
 - b. Most CCOs noted increased costs with the addition of these services
 - c. Almost universally, the CCOs do not want the current back guideline or back opioid guideline merged into a broader chronic pain guideline
- 2) For the proposed new coverage of chronic pain conditions:
 - a. Most CCOs are concerned about the increased cost of the nonpharmacological services for these conditions as well as significant concerns about the cost of Lyrica and other medications that would be covered if these conditions become funded
 - b. Most CCOs do not want non-opioid medications addressed in any chronic pain guideline
 - c. The CCOs were mixed on whether they thought coverage for fibromyalgia and chronic pain would improve the health of their patients or simplify administration
 - d. Nearly all responding CCOs were interested in incorporating Oregon opioid prescribing guidelines (acute and chronic)

CEBP MED report on opioid tapering take home points:

- 1) Overall quality of the evidence is very low
- 2) Overall, no change in conclusions since previous review
 - a. Findings suggested that pain, function, and quality of life might improve during and after opioid discontinuation or dose reduction
 - b. Scant evidence on harms associated with tapering strategies
- 3) Adverse events—mortality, suicide or overdose
 - a. 5 studies in the Frank review included adverse events
 - i. 1 opioid-related overdose death in a patient in a buprenorphine treatment program (after discontinuation of buprenorphine) out of a total of 5 studies (no N given)

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- b. A retrospective cohort study conducted in a VA population whose opioid therapy was discontinued by their clinician (primarily for aberrant behaviors) reported that 12% of the cohort had documented suicidal ideation and nonfatal suicidal self-directed violence (SSV) in the 12 months after opioid discontinuation
 - i. This study identified Hispanic ethnicity (adjusted odds ratio [OR] 7.25 (95% CI 1.96–27.18), PTSD diagnosis: 2.56 (1.23–5.32), and psychotic-spectrum disorder diagnoses (OR 3.19; 95% CI 1.14 to 8.89) were correlated with suicidal ideation and SSV in the 12 months following clinician-initiated opioid discontinuation.
 - c. Other new studies did not report information on serious adverse events such as mortality, suicide, or overdose events.
- 4) Adverse events—opioid withdrawal symptoms
- a. In the systematic review by Frank et al., 18 studies (3 fair and 15 poor methodological quality) reported opioid withdrawal symptoms. Rates of withdrawal symptoms ranged widely across the studies (0% to 100%).
 - b. The new studies we identified for this update did not provide information on withdrawal symptoms experienced by patients receiving the interventions.
- 5) Taper length
- a. Not able to draw any conclusions regarding rapid versus slow tapering.
- 6) Patient-initiated vs nonpatient-initiated tapering
- a. Very little information found on this issue. In almost all of the studies included in the previous MED report and in this update, patients had some autonomy in the decision to taper their opioids.
 - b. VA database study found that the reason for discontinuation (patient-initiated vs. clinician-initiated) was not correlated with pain score trajectory.
 - c. Demidenko et al. studied clinician-initiated discontinuation of opioids
 - i. Approximately 75% of the clinician-discontinued patient group had opioids stopped because of aberrant behaviors such as abnormal urine drug test results, opioid diversion, and drug misuse.
 - ii. Of the total sample of 509 patients, 59 had suicidal ideation or SSV documented in their charts; 47 had suicidal ideation alone, and 12 had SSV. Half of these patients attempted suicide with overdoses of prescription medications, primarily benzodiazepine drugs. Fifteen of the 59 patients had previous suicidal ideation or SSV events before discontinuation of opioid therapy.
 - a. 1 new study was identified that compared mandatory opioid dose reduction in a health system in Washington to usual care

The researchers found no indication that patients in the intervention clinics had clinically meaningful differences in pain intensity, interference with activities and enjoyment of life, or depressive symptoms compared with control group patients.

Additional important information/resources

- A. Oregon Acute Opioid Prescribing Guidelines
<https://www.oregon.gov/oha/PH/PREVENTIONWELLNESS/SUBSTANCEUSE/OPIOIDS/Documents/Acute-Prescribing-Guidelines.pdf>
- B. Oregon Chronic Opioid Prescribing Guidelines
<https://www.oregon.gov/oha/PH/PREVENTIONWELLNESS/SUBSTANCEUSE/OPIOIDS/Documents/Chronic-Opioid-Prescribing-Guidelines.pdf>

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- C. Oregon Opioid Prescribing Guidelines for Dentists
<https://www.oregon.gov/oha/PH/PREVENTIONWELLNESS/SUBSTANCEUSE/OPIOIDS/Documents/taskforce/oregon-opioid-prescribing-guidelines-dentists.pdf>
- D. Institute for Chronic Pain, description of centralized pain syndromes
<http://www.instituteforchronicpain.org/understanding-chronic-pain/what-is-chronic-pain/neuromatrix-of-pain>

Fibromyalgia guideline issue

HERC staff have noted that action needs to be taken on current Prioritized List fibromyalgia guideline. This guideline was developed based on evidence reviews conducted in 2008 and 2013, as well as expert input. The guideline largely mirrors the current CPTF proposal, with an additional sentence: "Use of opioids should be avoided due to evidence of harm in this condition." This sentence was added to the guideline based on expert input which indicated that opioids for fibromyalgia actually exacerbated the condition and therefore were a source of harm. Subsequently, Cochrane has conducted a systematic review of oxycodone for fibromyalgia published in 2016 which showed no evidence of benefit. Kim Jones, PhD has previously testified to the CPTF regarding the possible benefits of tramadol, a type of opioid, for treatment of fibromyalgia. The OHA Pharmacy and Therapeutics Committee recently completed a review of tramadol for fibromyalgia and found no evidence of benefit for this medication.

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Staff-introduced changes

Since the Chronic Pain Task Force (CPTF) completed their proposal in December, HERC staff has considered late public testimony, revisited state and national guidelines, and held extensive internal discussions. Based on these considerations, HERC staff has several proposed changes to the CPTF proposal to bring forward for VBBS consideration.

These changes include

- 1) Remove the suggestion to HERC to conduct a multi-sector intervention review for Tai Chi for chronic pain conditions. Such a review would require a large amount of staff resources. Encouragement for coverage for Tai Chi could be addressed by simply adding it to the list of services that should be covered “if available.” HERC staff received confirmation from OHA that this section of services should have “no wrong door,” meaning that they can be paid for with medical services funds or health related services funds by the CCOs.
- 2) There were concerns about using the term “compendia” for non-opioid medications raised by CCOs. In further discussions with P&T, HERC staff and P&T staff concluded that the entire statement “The medication is FDA approved or supported by compendia for treatment of chronic, non-neuropathic pain” should be removed. This statement does not add much to the guideline effect, as CCO contracts already contain similar wording; however, the clause is a source of confusion.
- 3) The PEG assessment scale was added to the list of examples for validated instruments for evaluation of the effectiveness of opioids. This change is based on the statement from the CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016: “Experts agreed that clinicians may use validated instruments such as the three-item “Pain average, interference with Enjoyment of life, and interference with General activity” (PEG) Assessment Scale to track patient outcomes.”
- 4) Removal of “centralized pain syndrome” from the new line guideline. This is not a formal diagnosis and does not have accepted diagnostic criteria. Use of this term is confusing to patients and providers and could be a source of variation in how the guideline is implemented by various CCOs. Staff feels that a patient with centralized pain syndrome would likely not receive functional benefit from opioids, and in that case would fail to meet the opioid prescribing criteria in the guideline. Therefore, further calling out of this diagnosis is not required to follow the CPTF intent.
- 5) Wording was added to the proposed new guideline to allow some discretion in provider management of patients on concurrent benzodiazepines and opioids.
- 6) Wording was changed in the proposed new guideline section regarding the need to taper patients on opioids over 90 MED, due to a desire to allow some provider discretion in patient management. The new proposed wording is based on the Oregon Opioid Prescribing Guidelines.
- 7) Wording was added to the opioid section of the new guideline and to the opioid for back conditions guideline clarifying that a taper can be slowed or paused if the prescribing provider feels that the clinical situation justifies such action.
- 8) Addition of wording requiring behavioral health evaluation and management during opioid tapers in both the new guideline and the back conditions opioid guideline. This change is in

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response to public testimony expressing concerns for mental health issues, including suicidality, that might be brought out by the opioid taper process if the patient requires such tapering.

Additional requests from stakeholders include:

- 1) Information on the number of patients who would be affected by the proposed changes to the Prioritized List. Staff is working on obtaining these numbers and will present them in the formal Powerpoint presentation at the meeting.
- 2) A summary of evidence reviewed for opioids in the treatment of fibromyalgia. The Pharmacy and Therapeutics Committee staff have prepared a formal evidence review on this topic which is included in the packet. Expert input brought additional literature to P&T staff attention and is included in this review if it met inclusion criteria.
- 3) OHA create a plan to monitor outcomes of the changes to coverage based on the CPTF changes. HERC staff will work with OHA staff to create an evaluation plan.
- 4) Clarification for the rationale for why non-opioid medications need evidence of a 15% improvement in function but opioids medications need a 30% improvement.
 - a. Coverage guidance criteria for the HERC generally uses a 15% improvement in function as a cut off for clinically significant change
 - b. The CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016 used the following: “Clinically meaningful improvement has been defined as a 30% improvement in scores for both pain and function.”
 - c. A higher threshold is appropriate in a case like this due to the known harms associated with opioid therapy in order to ensure benefits outweigh harms at a similar level compared to treatments without significant harms.

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Chronic Pain Taskforce Revised Proposal for HERC consideration with additional staff suggestions:

- 1) Create a new line for five chronic pain conditions and fibromyalgia for the 2020 Biennial Review as shown below
- 2) Adopt a new guideline for treatments included on this line as shown below
- 3) Score this new line as shown below
 - a. Proposed ranking would put this line in the funded region, around line 443 (near the funding line, which is currently below line 469).
- 4) Modify line 528 FIBROMYALGIA, CHRONIC FATIGUE SYNDROME AND RELATED CONDITIONS as shown below
 - a. Remove all diagnoses other than chronic fatigue syndrome and modify line title
- 5) Modify GUIDELINE NOTE 56, NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE as shown below
 - a. Matches changes in the new chronic pain conditions guideline
 - b. Removes obsolete table
- 6) Modify GUIDELINE NOTE 60, OPIOIDS FOR CONDITIONS OF THE BACK AND SPINE as shown below
 - a. Modifies the paragraph on tapering for chronic opioid use to match wording in new chronic pain conditions guideline
 - b. Removes flares of chronic pain as an indication for opioids
- 7) Modify GUIDELINE NOTE 92, ACUPUNCTURE as shown below
 - a. Adds the new chronic pain line to the guideline
 - b. **consider wording limiting all acupuncture to 30 visits a year to mirror PT guideline**
- 8) Delete GUIDELINE NOTE 135, FIBROMYALGIA
 - a. Components are all incorporated into the new guideline

Note: HERC staff suggested changes to the Chronic Pain Taskforce's recommendations are shown in purple.

LINE: XXX

CONDITION: FIBROMYALGIA, CHRONIC PAIN SYNDROME, AND RELATED CONDITIONS

TREATMENT: LIMITED PHYSICAL MODALITIES, COGNITIVE BEHAVIORAL THERAPY, MEDICAL THERAPY

ICD-10: G89.21 (Chronic pain due to trauma), G89.28 (Other chronic postprocedural pain), G89.29 (Other chronic pain), G89.4 (Chronic pain syndrome), M79.7 (fibromyalgia)

CPT: 90785, 90832-90840, 90853 (psychotherapy—for CBT and ACT), 96150-96155 (Health and behavior assessment and intervention), 97110-97124, 97140-97168, 97530, 97535 (PT/OT), 97810-97814 (acupuncture), 98966-98969, 99051, 99060,99070,99078,99201-99215,99281-99285,99304-99337,99340-99404,99408-99449,99487-99490,99495,99496,99605-99607 (medical office visits, including ER and SNF)

HCPCS: G0157-G0160 (PT/OT assistant), G0396-G0397 (alcohol and substance abuse screening), G0463-G0467,G0469,G0470 (FQHC care), G0490, G0511-G0513 (RFQHC care), G0514 (prolonged office visit)

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GUIDELINE NOTE XXX TREATMENT OF FIBROMYALGIA, CHRONIC PAIN SYNDROME AND RELATED CONDITIONS

Lines XXX

Chronic pain syndrome (ICD-10 G89.4), chronic pain due to trauma (ICD-10 G89.21), other chronic postprocedural pain (ICD-10 G89.28), other chronic pain (ICD-10 G89.29), and fibromyalgia (ICD-10 M79.7) are included on line XXX when symptoms have been present for at least 3 months.

The following treatments are included on line XXX:

- Office evaluation, consultation and education.
 - Pain education, if done, should include but not be limited to sleep, nutrition, stress reduction/mood, exercise, and knowledge of pain as a biopsychosocial phenomenon. All providers [seeing/managing](#) chronic pain patients should be trained in pain science (e.g., a contemporary understanding of the central and peripheral nervous system in chronic pain), motivational interviewing, culturally sensitive care, and trauma informed care. Care should be multidisciplinary and focus on active therapies.
- Cognitive behavioral therapy (CBT). The necessity for CBT should be re-evaluated every 90 days and coverage will only be continued if there is documented evidence of decreasing depression or anxiety symptomatology, improved ability to work/function, increased self-efficacy, or other clinically significant, objective improvement.
- The following therapies, when available, may be provided: adaptive and restorative yoga, [Tai Chi](#), mindfulness training, massage, supervised exercise therapy (land based and aquatic), intensive interdisciplinary rehabilitation. HCPCS S9451 is only included on Line XXX for the provision of yoga or supervised exercise therapy.
- A total of 30 visits per year of any combination of the following therapies when available and medically appropriate. These therapies are only included on these lines if provided by a provider licensed to provide the therapy and when there is documentation of measurable clinically significant progress toward the therapy plan of care goals and objectives using evidence-based objective tools. Once the pre-determined goals of care have been achieved, an additional two visits may be authorized for maintenance therapy to maintain these improvements. These 30 visits count toward the visit totals in GUIDELINE NOTE 56 NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE if the patient has comorbid back or spine conditions.
 - 1) Rehabilitative therapy (physical and/or occupational therapy), if provided according to Guideline Note 6 REHABILITATIVE AND HABILITATIVE THERAPIES. Rehabilitation services provided under this guideline also count towards visit totals in Guideline Note 6. CPT 97124 is included in this category.
 - 2) Acupuncture

Non-opioid medications are only included on line XXX if all of the following apply:

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- 1) ~~The medication is FDA approved or supported by compendia for treatment of chronic, non-neuropathic pain.~~
- 2) The patient is also being treated with active therapy (e.g., physical therapy, CBT) or is continuing maintenance of self-management strategies learned from such therapy.
- 3) The benefit of non-opioid medication is re-evaluated at least every 90 days and medications are only continued if there is documented evidence of initial improvement of function of at least fifteen percent as compared to baseline based on a validated tool (e.g., Pain average, interference with Enjoyment of life, and interference with General activity” (PEG) Assessment Scale, Oswestry, SF-MPQ, MSPQ), and function is maintained thereafter. Less frequent monitoring may be appropriate for certain medications after safety and efficacy are established.

Opioids for chronic pain syndrome (when not representing centralized pain syndrome), chronic pain due to trauma, other chronic postprocedural pain, and other chronic pain

Chronic opioids (>90 days) are only covered for chronic pain syndrome (ICD-10 G89.4; ~~when not representing centralized pain syndrome~~), chronic pain due to trauma (ICD-10 G89.21), other chronic postprocedural pain (ICD-10 G89.28), and other chronic pain (ICD-10 G89.29) when all of the following are met:

- In alignment with the Oregon Opioid Prescribing Guideline (2017-2018 version) <https://www.oregon.gov/oha/PH/PREVENTIONWELLNESS/SUBSTANCEUSE/OPIOIDS/Documents/taskforce/oregon-opioid-prescribing-guidelines.pdf>
- Appropriate risk assessment has been performed (e.g., Opioid Risk Assessment Tool)
- PDMP checked at least annually and shows no aberrant behavior
- No concurrent prescribing of benzodiazepines without extenuating circumstances
- Urine drug testing is performed at least once per year and is appropriate
- No illicit drug use or active substance use disorder (excluding tobacco)
- ~~MED < 50, or between 50 and 90 with extenuating circumstances [MED=morphine equivalent daily dose]. For patients at or above 50 MED, every attempt should be made to taper according to the taper guidelines (ideally to MED <50)~~ Careful reassessment of the evidence of individual benefits and risks should be undertaken for dosages > 50 MED. Dosages >90 MED should be avoided or carefully justified.
- Initial functional improvement has been documented of at least 30%, and function is maintained throughout the prescribing period
- Comorbid mental health disorders are appropriately addressed
- No additional opioids are prescribed for flares of the chronic pain condition, although opioids may be prescribed separately for other acute injuries or surgeries as clinically appropriate
- Prescriber has updated opioid prescribing CME and ideally has completed the Oregon Pain Management Commission (OPMC) OPMC pain module
- Patient and provider have assessed the relative risks and benefits of therapy and agree benefits outweigh risks, and have completed a material risk notice <https://www.oregon.gov/omb/OMBForms1/material-risk-notice.pdf>
- The patient be prescribed the patient pain education module through OPMC when it becomes available
- When prescribed with nonpharmacologic treatment options for managing pain

Opioid tapering for fibromyalgia and ~~other chronic pain conditions on this line~~ patients failing to meet the opioid prescribing criteria above:

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Opioids are not intended for inclusion on this line for the following conditions/situations due to the evidence for harm:

- fibromyalgia
- ~~centralized pain syndrome (sometimes coded as chronic pain syndrome, ICD-10-G89.4)~~
- patients who fail to meet the guideline requirements regarding opioids above who have chronic pain syndrome (~~when not representing centralized pain syndrome~~), chronic pain due to trauma, other chronic postprocedural pain, and other chronic pain conditions included on this line

If a patient is already receiving chronic opioid therapy for these conditions/situations, then tapering is indicated. Opioid tapering should be done on an individualized basis which includes a taper goal of zero. Tapering should be unidirectional with a shared goal set by the patient and provider, generally with a 5-10% decrease monthly, and can be paused or slowed if the prescriber believes this is medically appropriate based on the patient's overall status. Taper plans should include nonpharmacological treatment strategies for managing the patient's pain. During the taper, behavioral health conditions need to be regularly assessed and appropriately managed. In some situations (e.g., in the setting of active substance use disorder, history of opioid overdose, aberrant behavior), more rapid tapering or transition to medication assisted treatment may be appropriate and should be directed by the prescribing provider. If a patient has developed opioid use disorder, treatment is included on Line 4 SUBSTANCE USE DISORDER.

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Line Scoring

Line 401 CONDITIONS OF THE BACK AND SPINE (current scoring shown)

Category: 7
HL: 4
Suffering: 3
Population effects: 0
Vulnerable population: 0
Tertiary prevention: 2
Effectiveness: 3
Need for service: 0.8
Net cost: 2
Score: 432
Current line placement: 401

Line XXX FIBROMYALGIA, CHRONIC PAIN SYNDROME AND RELATED CONDITIONS

Category: 7
HL: 4
Suffering: 3
Population effects: 0
Vulnerable population: 0
Tertiary prevention: 2
Effectiveness: 2
Need for service: 0.8
Net cost: 2
Score: 288
Approximate line placement: 443

Line 528 CHRONIC FATIGUE SYNDROME (current scoring of line FIBROMYALGIA, CHRONIC FATIGUE SYNDROME, AND RELATED DISORDERS shown)

Category: 7
HL: 4
Suffering: 3
Population effects: 0
Vulnerable population: 0
Tertiary prevention: 0
Effectiveness: 1
Need for service: 0.8
Net cost: 2
Score: 112
Current line placement: 528

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Line: 528

Condition: ~~FIBROMYALGIA, CHRONIC FATIGUE SYNDROME, AND RELATED DISORDERS~~ (See Guideline Notes 64,65,~~135~~)

Treatment: MEDICAL THERAPY

ICD-10: ~~G89.21,G89.28-G89.29,G89.4,M79.7~~,R53.82

CPT: 90785,90832-90840,90846-90853,93792,93793,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99487-99490,99495-99498,99605-99607

HCPCS: G0248-G0250,G0396,G0397,G0463-G0467,G0490,G0511,G0513,G0514

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GUIDELINE NOTE 56, NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE

Lines 361,401

Patients seeking care for back pain should be assessed for potentially serious conditions (“red flag” symptoms requiring immediate diagnostic testing), as defined in Diagnostic Guideline D4. Patients lacking red flag symptoms should be assessed using a validated assessment tool (e.g. STarT Back Assessment Tool) in order to determine their risk level for poor functional prognosis based on psychosocial indicators.

For patients who are determined to be low risk on the assessment tool, the following services are included on these lines:

- Office evaluation and education,
- Up to four total visits, consisting of the following treatments: OMT/CMT, acupuncture, and PT/OT. Massage, if available, may be provided as part of these four total visits.
- First line medications: NSAIDs, acetaminophen, and/or muscle relaxers. Opioids may be considered as a second line treatment, subject to the limitations on coverage of opioids in Guideline Note 60 OPIOIDS FOR CONDITIONS OF THE BACK AND SPINE. [See evidence table.](#)

For patients who are determined to be medium- or high risk on the validated assessment tool, as well as patients undergoing opioid tapers as in Guideline Note 60 OPIOIDS FOR CONDITIONS OF THE BACK AND SPINE, the following treatments are included on these lines:

- Office evaluation, consultation and education
 - Cognitive behavioral therapy (CBT). The necessity for CBT should be re-evaluated every 90 days and coverage will only be continued if there is documented evidence of decreasing depression or anxiety symptomatology, improved ability to work/function, increased self-efficacy, or other clinically significant, objective improvement.
 - Prescription and over-the-counter medications; opioid medications subject to the limitations on coverage of opioids in Guideline Note 60 OPIOIDS FOR CONDITIONS OF THE BACK AND SPINE. [See evidence table.](#)
 - The following evidence-based therapies, when available, may be provided: yoga, massage, supervised exercise therapy, intensive interdisciplinary rehabilitation. HCPCS S9451 is only included on Line 401 for the provision of yoga or supervised exercise therapy.
 - A total of 30 visits per year of any combination of the following evidence-based therapies when available and medically appropriate. These therapies are only included on these lines if provided by a provider licensed to provide the therapy and when there is documentation of measurable clinically significant progress toward the therapy plan of care goals and objectives using evidence based objective tools (e.g. Oswestry, Neck Disability Index, SF-MPQ, and MSPQ). [These 30 visits count toward the visit totals in GUIDELINE NOTE XXX TREATMENT OF FIBROMYALGIA, CHRONIC PAIN SYNDROME AND RELATED CONDITIONS if the patient has one or more of these comorbid chronic pain conditions.](#)
- 3) Rehabilitative therapy (physical and/or occupational therapy), if provided according to Guideline Note 6 REHABILITATIVE AND HABILITATIVE THERAPIES. Rehabilitation services provided under this guideline also count towards visit totals in Guideline Note 6. CPT 97124 is included in this category.
 - 4) Chiropractic or osteopathic manipulation
 - 5) Acupuncture

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Mechanical traction (CPT 97012) is not included on these lines, due to evidence of lack of effectiveness for treatment of back and neck conditions.

The development of this guideline note was informed by HERC coverage guidances on [Low Back Pain Non-Pharmacologic, Non-Invasive Intervention](#), [Low Back Pain, Pharmacological and Herbal Therapies](#). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

[delete the table below]

Evidence Table of Effective Treatments for the Management of Low Back Pain

| Intervention Category* | Intervention | Acute < 4 Weeks | Subacute & Chronic > 4 Weeks |
|---|--|--------------------|------------------------------------|
| Self-care | Advice to remain active | ● | ● |
| | Books, handout | ● | ● |
| | Application of superficial heat | ● | |
| Nonpharmacologic therapy | Spinal manipulation | ● | ● |
| | Exercise therapy | | ● |
| | Massage | | ● |
| | Acupuncture | | ● |
| | Yoga | | ● |
| | Cognitive-behavioral therapy | | ● |
| | Progressive relaxation | | ● |
| | | | |
| Pharmacologic therapy <small>(Carefully consider risks/harms)</small> | Acetaminophen | ● | ● |
| | NSAIDs | ●(▲) | ●(▲) |
| | Skeletal muscle relaxants | ● | |
| | Antidepressants (TCA) | | ● |
| | <i>Benzodiazepines**</i> | ●(▲) | ●(▲) |
| | <i>Tramadol, opioids**</i> | ●(▲) | ●(▲) |
| Interdisciplinary therapy | Intensive interdisciplinary rehabilitation | | ● |
| <ul style="list-style-type: none"> Interventions supported by grade B evidence (at least fair-quality evidence of moderate benefit, or small benefit but no significant harms, costs, or burdens). No intervention was supported by grade "A" evidence (good-quality evidence of substantial benefit). <p>▲ <i>Carries greater risk of harms than other agents in table.</i></p> | | | |

NSAIDs = nonsteroidal anti-inflammatory drugs; TCA = tricyclic antidepressants.

*These are general categories only. Individual care plans need to be developed on a case by case basis. For more detailed information please see: <http://www.annals.org/content/147/7/478.full.pdf>

**Associated with significant risks related to potential for abuse, addiction and tolerance. This evidence evaluates effectiveness of these agents with relatively short term use studies. Chronic use of these agents may result in significant harms.

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GUIDELINE NOTE 60, OPIOIDS FOR CONDITIONS OF THE BACK AND SPINE

Lines 346,361,401,527

Opioid medications are only included on these lines under the following criteria:

For acute injury, ~~acute flare of chronic pain~~, or after surgery:

- 1) During the first 6 weeks opioid treatment is included on these lines ONLY:
 - a) When each prescription is limited to 7 days of treatment, AND
 - b) For short acting opioids only, AND
 - c) When one or more alternative first line pharmacologic therapies such as NSAIDs, acetaminophen, and muscle relaxers have been tried and found not effective or are contraindicated, AND
 - d) When prescribed with a plan to keep active (home or prescribed exercise regime) and with consideration of additional therapies such as spinal manipulation, physical therapy, yoga, or acupuncture, AND
 - e) There is documented verification that the patient is not high risk for opioid misuse or abuse.
- 2) Treatment with opioids after 6 weeks, up to 90 days after the initial injury/~~flare~~/surgery is included on these lines ONLY:
 - a) With documented evidence of improvement of function of at least thirty percent as compared to baseline based on a validated tools (e.g. [Pain average, interference with Enjoyment of life, and interference with General activity” \(PEG\) Assessment Scale](#), Oswestry, Neck Disability Index, SF-MPQ, and MSPQ).
 - b) When prescribed in conjunction with therapies such as spinal manipulation, physical therapy, yoga, or acupuncture.
 - c) With verification that the patient is not high risk for opioid misuse or abuse. Such verification may involve
 - i) Documented verification from the state's prescription monitoring program database that the controlled substance history is consistent with the prescribing record
 - ii) Use of a validated screening instrument to verify the absence of a current substance use disorder (excluding nicotine) or a history of prior opioid misuse or abuse
 - iii) Administration of a baseline urine drug test to verify the absence of illicit drugs and non-prescribed opioids.
 - d) Each prescription must be limited to 7 days of treatment and for short acting opioids only
- 3) Chronic opioid treatment (>90 days) after the initial injury/~~flare~~/surgery is not included on these lines except for the taper process described below.

Transitional coverage for patients on long-term opioid therapy ~~as of July 1, 2016~~:

For patients ~~on covered chronic~~ [receiving long-term](#) opioid therapy ([>90 days](#)) for [conditions of the back and spine](#) ~~as of July 1, 2016, opioid medication is included on these lines only from July 1, 2016 to December 31, 2016. During the period from January 1, 2017 to December 31, 2017, continued coverage of opioid medications requires an individual treatment plan [which includes a taper plan developed by January 1, 2017 which includes a taper with an end to opioid therapy no later than January 1, 2018. Opioid tapering should be done on an individualized basis and include a taper goal to zero. Tapering should be unidirectional with a shared goal set by the patient and provider, generally with a 5-10% decrease monthly and can be paused or slowed if the prescriber believes this is medically appropriate based on the patient’s overall status.](#) Taper plans ~~must~~ [should](#) include nonpharmacological treatment strategies for managing the patient’s pain ~~based on Guideline Note 56 NON-INTERVENTIONAL~~~~

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~~TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE.~~ During the taper, behavioral health conditions need to be regularly assessed and appropriately managed. In some situations (e.g., in the setting of active substance use disorder, history of opioid overdose, aberrant behavior), more rapid tapering or transition to medication assisted treatment may be appropriate and should be directed by the prescribing provider. If a patient has developed ~~dependence and/or addiction related to their opioids~~ opioid use disorder, treatment is ~~available~~ included on Line 4 SUBSTANCE USE DISORDER.

GUIDELINE NOTE 92, ACUPUNCTURE

Lines 1,5,202,361,401,409,461,538

Inclusion of acupuncture (CPT 97810-97814) on the Prioritized List has the following limitations:

Line 1 PREGNANCY

Acupuncture pairs on Line 1 for the following conditions and codes.

Hyperemesis gravidarum

ICD-10-CM: O21.0, O21.1

Acupuncture pairs with hyperemesis gravidarum when a diagnosis is made by the maternity care provider and referred for acupuncture treatment for up to 12 sessions of acupuncture/acupressure per pregnancy.

Breech presentation

ICD-10-CM: O32.1

Acupuncture (and moxibustion) is paired with breech presentation when a referral with a diagnosis of breech presentation is made by the maternity care provider, the patient is between 33 and 38 weeks gestation, for up to 6 sessions per pregnancy.

Back and pelvic pain of pregnancy

ICD-10-CM: O99.89

Acupuncture is paired with back and pelvic pain of pregnancy when referred by maternity care provider/primary care provider for up to 12 sessions per pregnancy.

Line 5 TOBACCO DEPENDENCE

Acupuncture is included on this line for a maximum of 12 sessions per quit attempt up to two quit attempts per year; additional sessions may be authorized if medically appropriate.

Line 202 CHRONIC ORGANIC MENTAL DISORDERS INCLUDING DEMENTIAS

Acupuncture is paired with the treatment of post-stroke depression only. Treatments may be billed to a maximum of 30 minutes face-to-face time and limited to 12 total sessions per year, with documentation of meaningful improvement; patients may have additional visits authorized beyond these limits if medically appropriate.

Line 361 SCOLIOSIS

Acupuncture is included on this line with visit limitations as in Guideline Note 56 NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE.

Line 401 CONDITIONS OF THE BACK AND SPINE

Acupuncture is included on this line with visit limitations as in Guideline Note 56 NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE.

Line 409 MIGRAINE HEADACHES

Acupuncture pairs on Line 409 for migraine (ICD-10-CM G43.0, G43.1, G43.5, G43.7, G43.8, G43.9), for up to 12 sessions per year.

[Line XXX FIBROMYALGIA, CHRONIC PAIN SYNDROME AND RELATED CONDITIONS](#)

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Acupuncture is included on this line with visit limitations as in Guideline Note XXX TREATMENT OF FIBROMYALGIA, CHRONIC PAIN SYNDROME AND RELATED CONDITIONS

Line 461 OSTEOARTHRITIS AND ALLIED DISORDERS

Acupuncture pairs on Line 461 for osteoarthritis of the knee only (ICD-10-CM M17), for up to 12 sessions per year.

*Line 538 TENSION HEADACHES

Acupuncture is included on Line 538 for treatment of tension headaches (ICD-10-CM G44.2), for up to 12 sessions per year.

The development of this guideline note was informed by a HERC [coverage guidance](http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx). See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

*Below the current funding line

~~GUIDELINE NOTE 135, FIBROMYALGIA~~

~~Line 528~~

~~Fibromyalgia (ICD-10-CM M79.7) treatment should consist of a multi-modal approach, which should include two of more of the following:~~

- ~~A) medications other than opioids~~
- ~~B) exercise advice/programs~~
- ~~C) cognitive behavioral therapy.~~

~~Care should be provided in the primary care setting. Referrals to specialists are generally not required. Use of opioids should be avoided due to evidence of harm in this condition~~

Indication Review: Fibromyalgia

Date of Review: January 2019

End Date of Literature Search: 10/05/2018

Purpose for Review:

To evaluate safety and efficacy pharmacological treatments for fibromyalgia as requested by the Health Evidence Review Commission (HERC). Medical therapy for fibromyalgia is currently not funded by the Oregon Health Authority (OHA). The review focuses specifically on treatment of fibromyalgia as non-analgesics for treatment of chronic non-cancer pain or neuropathic pain have been reviewed previously.^{1,2} Evidence for tramadol in chronic non-cancer pain was also reviewed in 2017,³ and evidence for opioid analgesics was last reviewed in 2016.⁴

Research Questions:

1. What is the efficacy and safety of pharmacotherapy for treatment of fibromyalgia compared to placebo, other pharmacological therapies, or non-pharmacological treatments?
2. Are there any subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) for which pharmacotherapy for fibromyalgia is more effective or associated with more long-term adverse effects?

Conclusions:

- There is no moderate or high strength evidence for any pharmacological treatment compared to placebo or other therapy. Like many other conditions for chronic pain, evidence supporting benefit of long-term pharmacological treatment for fibromyalgia is limited, efficacy of pharmacotherapy is relatively modest, and clinical trials often document a large placebo response upon evaluation of symptom improvement. Pharmacological interventions with the most evidence of benefit include duloxetine, milnacipran, and pregabalin, but applicability to a broader population is limited. In many trials, patients with comorbid medical conditions, particularly mental health conditions, were excluded. Similarly, many patients with a placebo response during run-in periods were excluded from trials. The strongest available evidence for efficacy outcomes for fibromyalgia drugs was of low strength meaning there is limited confidence that the estimated effects in the studies reflect the true effect, and further research is likely to change the estimated effect.
- There is low strength evidence that, compared to placebo, milnacipran or duloxetine may improve pain symptoms as evaluated by patient global impression of improvement or change (PGI-I or PGIC) of much or very much improved, 30% improvement in pain, pain intensity, and disability.⁵ Scores of much or very much improved and 30% improvement in pain typically correspond to an average 2 point improvement from baseline on a 0 to 10 numeric rating scale.⁶ The number needed to treat (NNT) for a minimal pain improvement with an average treatment duration of less than 3 months ranged from 5-10 depending on the outcome evaluated.⁵
- Milnacipran or duloxetine may have no clinical improvement for pain relief of 50% or more, sleep, fatigue, depression, cognitive disturbances, anxiety or quality of life (low strength of evidence). The NNT was 11 for pain relief of 50% or more (typically corresponding to a change of at least 3-4 points on a 0-10 rating scale), and while some other outcomes did achieve statistically significant differences from placebo, estimates were below the threshold for what would be considered a detectable clinically significant change.⁵

- There is low strength evidence that, compared to placebo, pregabalin may improve outcomes of pain relief of more than 50%, pain relief of more than 30%, and pain improvement as evaluated by a PGIC score of much or very much improved. The estimated NNT varied depending on dose and outcome, but ranged from 7 to 22.
- There is insufficient evidence on long-term use of pharmacological therapy for treatment of fibromyalgia, and it is unclear if modest improvements in pain outcomes would be sustained over time. The average duration of most trials was less than 3 months and few trials assessed outcomes beyond 6 months.
- Adverse effects more common with pregabalin compared to placebo included somnolence (number needed to harm [NNH] 7), dizziness (NNH 3), weight gain (NNH 18) and peripheral edema (NNH 19; low strength evidence). SNRIs (duloxetine, milnacipran and desvenlafaxine) were associated with an increased incidence of nausea (NNH 6) and somnolence (NNH 20).
- Evidence of benefit or harms for other pharmacological treatments (including tricyclic antidepressants, gabapentin, and tramadol) was insufficient. For example, while tricyclic antidepressants such as amitriptyline have historically been utilized for treatment of fibromyalgia, available evidence in randomized control trials has high risk of bias making estimates of the treatment effects uncertain.^{7,8} Overall, evidence for other pharmacological treatments was limited by significant risk of bias, small sample sizes, and/or limited applicability to patients with comorbid medical conditions.
- There is insufficient evidence to determine relative efficacy of pharmacological treatment compared to non-pharmacological therapies.
- Guidelines for fibromyalgia recommend patient education and focus primarily on nonpharmacological treatments such as exercise to improve symptoms of fibromyalgia. Pharmacotherapy and other non-pharmacotherapy options (e.g., cognitive behavioral therapy, multicomponent therapy, acupuncture, hydrotherapy, meditative movement, and mindfulness-based stress reduction) are recommended as second-line treatment options. Guidelines note that benefits of pharmacological treatments are relatively modest and, as magnitude of benefits are approximately equivalent to incidence of adverse effects from treatment, risks of therapy should be weighed against potential benefits.

Recommendations:

- No further research, review, or policy changes needed at this time.

Background:

Fibromyalgia is a chronic non-inflammatory pain disorder often associated with symptoms such as fatigue, depressed mood and cognitive dysfunction.⁹ Pain associated with fibromyalgia is typically widespread, diffuse, and may become progressively more persistent over time. Diagnosis is based primarily on history, physical exam, and absence of other disorders which would explain the chronic pain.⁹ The cause of fibromyalgia is unknown, but is thought to be related to abnormal pain processing in the nervous system and abnormal stress response in the hypothalamic pituitary adrenal axis. Estimated prevalence of fibromyalgia in North America is approximately 1-3% of patients and most commonly affects women. Risk factors which may be associated with increased incidence of fibromyalgia include physical trauma or injury, physical or sexual abuse, stress, infection, and sleep problems. Fibromyalgia is also commonly associated with a variety of comorbid conditions such as autoimmune disorders, psychiatric disorders, and functional somatic syndromes.

Goals of treatment include symptom improvement, functional improvement, enhanced patient self-management and self-efficacy, and management of comorbid conditions.⁹ Recommended therapy for treatment of fibromyalgia includes self-management strategies, non-pharmacological approaches as well as pharmacological treatment. Only 3 pharmacological agents are FDA-approved for treatment of fibromyalgia (**Table 1**). A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies. Other pharmacological agents which have been used off-label for treatment of

fibromyalgia include other pain medications such as opioids or acetaminophen, antidepressants such as amitriptyline or venlafaxine, other anticonvulsants such as gabapentin, and muscle relaxants like cyclobenzaprine.⁹

Table 1. Indications and Dosing for Drugs FDA-approved for Fibromyalgia¹⁰⁻¹²

| Drug Name | Indication(s) | Strength/Route | Fibromyalgia Dose and Frequency |
|---|--|---|--|
| Duloxetine (Cymbalta® and generics) | <ul style="list-style-type: none"> • Fibromyalgia • Generalized anxiety disorder • Major depressive disorder (unipolar) • Musculoskeletal pain, chronic • Neuropathic pain associated with diabetes mellitus | <ul style="list-style-type: none"> • 20, 30, 40, 60 mg ER capsules | Initial: 30 mg once daily Max: 60 mg once daily |
| Milnacipran (Savella®) | <ul style="list-style-type: none"> • Fibromyalgia | <ul style="list-style-type: none"> • 12.5, 25, 50 and 100 mg oral tablets | Initial: 12.5 mg on day 1 titrated to 50 mg BID Max: 100 mg BID |
| Pregabalin (Lyrica®) | <ul style="list-style-type: none"> • Fibromyalgia • Neuropathic pain associated with diabetes mellitus • Neuropathic pain with spinal cord injury • Partial-onset seizures, adjunctive therapy • Postherpetic neuralgia | <ul style="list-style-type: none"> • 25, 50, 75, 100, 150, 200, 225, 300 mg oral capsule • 20 mg/mL oral solution • 82.5, 165, 330 mg ER oral tablet | Initial: 75 mg IR capsules BID Max: 225 mg IR capsules BID |

Abbreviations: BID = twice daily; ER = extended release; IR = immediate release

Recently published guidelines from the European League Against Rheumatism (EULAR) focus on patient education and graded exercise as recommended first-line treatments to improve pain, sleep, function, and mood (strong recommendation).¹³ Second-line therapies include both pharmacological and non-pharmacological management and were based on weak recommendations.¹³ Second-line non-pharmacological therapies included cognitive behavioral therapy, multicomponent therapy, acupuncture, hydrotherapy, meditative movement, and mindfulness-based stress reduction which may be considered upon inadequate improvement to exercise.¹³ Recommendations for second-line pharmacological management included only low-dose amitriptyline, duloxetine, milnacipran, pregabalin, and cyclobenzaprine.¹³ Authors note that effect size for most pharmacological treatments is relatively modest, and the medications listed above are not licensed by the European Medical Agency for treatment of fibromyalgia because the small benefits did not outweigh risks associated with treatment.^{5,13,14} Canadian guidelines also include nonpharmacological therapies as a core modality of treatment with a focus on regular physical activity and incorporation of good coping mechanisms.¹⁵ Pharmacotherapy may be considered based on treatment response, but risks of therapy should be balanced against benefits.¹⁵ As with many other chronic pain conditions, efficacy of treatment with medications is relatively modest and should be weighed against the risks of therapy. For example, while pregabalin is FDA-indicated for multiple neuropathic conditions including fibromyalgia, it is also a controlled substance and may have some risk of dependence, abuse, or misuse.¹⁶

Many patient-reported scales are used to evaluate both functional improvement and pain severity in patients with chronic pain. Pain improvement is often evaluated using a variety of different symptoms scales in clinical trials. Common scales to assess pain symptoms include the Brief Pain inventory (BPI; range 0-10), numeric rating scales (range 0-10), visual analog scale (typically scale 0-10 or 0-100), fibromyalgia impact questionnaire (range 0-100), and patient global impression of improvement (range 1-7). Minimally clinically important differences for these scales can vary based on the condition and with acute versus chronic

pain, due to the subjective nature of these assessments, and there is no definitive definition of what may be considered a clinically important difference for an individual patient. However, consensus recommendations have been proposed for thresholds which may be considered clinically significant for patients with fibromyalgia or chronic pain. Generally, improvements of 20% on numeric rating scales have been considered of minimal benefit and changes of greater than 30% have been defined as moderate improvement in symptoms.⁶ Upon comparison of rating scales, a score of 2 on the PGI-I scale defined as being “much better” correlated with improvements of approximately 30% improvement from baseline or a 2 point improvement on the 11-point brief pain inventory.⁶ Similarly, a score of 1 on the PGI-I scale defined as “very much better” correlated with improvements of approximately 50% improvement in pain or a 3-4 point improvement on the 11-point brief pain inventory.^{6,17} Measurements for functional improvement include the Oswestry Disability Index (range 0-100), and the Roland-Morris Disability Questionnaire (range 0-24). Current literature for treatment of pain defines 10% of patients (corresponding to a NNT or NNH of 10) as a magnitude of benefit which might be considered clinically significant for a population of patients.⁵ However, estimates of clinical importance based on the magnitude of benefit for a population of patients are subjective and may vary depending on the risks and benefits for a particular patient.

In the OHP, mental health drugs including duloxetine and other antidepressants are carved-out and do not currently require prior authorization. Both milnacipran (Savella[®]) and pregabalin require PA to ensure medications are used for a funded diagnoses. Use of pregabalin for chronic neuropathic pain is also limited to patients who have intolerance, contraindications, or have tried and failed gabapentin therapy.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

A Cochrane review evaluated efficacy of pregabalin compared to placebo for treatment of fibromyalgia.¹⁸ The review included 8 RCTs with 3283 patients.¹⁸ Three of the included studies had unclear randomization methods, 4 had unclear allocation concealment, 3 had unclear blinding methods, and 5 used last observation carried forward for missing data which may increase risk of bias and overestimate the effects of treatment.¹⁸ Only 2 studies involved more than 200 participants and only one study evaluated treatment for 6 months.¹⁸ Because the difference compared to placebo for most outcomes was relatively modest, these methodological limitations could have had a significant impact on the findings this review and may lead to overestimates of treatment effect. The majority of patients were women, white, age 47-50 years old, and with severe pain symptoms. For pain improvement of at least 50%, patients treated with pregabalin 300 mg (22% vs. 14%; NNT 14; RR 1.51, 95% CI 1.20 to 1.90), 450 mg (22% vs. 14%; NNT 9; RR 1.74, 95% CI 1.44 to 2.13), and 600 mg (24% vs. 15%; NNT 11; RR 1.64, 95% CI 1.28 to 2.10) had a statistically significant improvement compared to placebo.¹⁸ A 30% improvement in pain was also shown for 300 mg (39% vs. 28%; NNT 9; RR 1.4, 95% CI 1.2 to 1.6), 450mg (43% vs. 29%; NNT 7; RR 1.5, 95% CI 1.3 to 1.7), and 600 mg (39% vs. 28%; NNT 9; RR 1.4, 95% CI 1.2 to 1.6) compared to placebo. Similar results were noted with PGIC scores of much improved corresponding to an approximate 2 point improvement (36-40% vs. 27%; NNT 7-11) or very much improved corresponding to an approximate 3-4 point improvement (12-17% vs. 7-10%; NNT 12-22).¹⁸ Discontinuation due to lack of efficacy was

statistically more common with placebo (9-10%) than pregabalin 300-600 mg daily (2-4%; NNT 15-18), but discontinuation due to adverse events was more common with pregabalin 300-600 mg (16-28%) compared to placebo (9-11%; NNH 6-17) with a dose-related increase in discontinuations due to adverse events.¹⁸ Common adverse events which were statistically more frequent with pregabalin compared to placebo included somnolence (23% vs. 10%; NNH 7), dizziness (38% vs. 11%; NNH 3), weight gain (9% vs. 3%; NNH 18), and peripheral edema (8% vs. 2%; NNH 19).¹⁸ Two randomized discontinuation trials also evaluated maintenance of benefit in patients with an initial response to pregabalin. Of the 1492 patients given pregabalin, 34% of patients discontinued treatment during dose titration, and only 46% of patients (n=687) were enrolled in the study and had a 50% improvement in pain after 6 weeks of treatment.¹⁸ These patients were randomized to continue pregabalin treatment or transition to placebo. At 13 to 26 weeks after randomization, more patients given pregabalin had a 30% pain improvement from baseline compared to patients given placebo (40% vs. 20%; RR 1.9, 95% CI 1.5 to 2.4).¹⁸ However, only 14% of patients initially enrolled in the study completed the randomized phase of the trial with maintenance of therapeutic response (9.1% with pregabalin vs. 4.8% with placebo) indicating that only a very small proportion of patients may actually benefit from long-term treatment.¹⁸

A 2018 Cochrane review evaluated the efficacy and safety of SNRIs for treatment of fibromyalgia.⁵ The review included 7903 participants in 18 studies of duloxetine (n=7), milnacipran (n=9), and desvenlafaxine (n=1).⁵ Of the studies included, 7 were evaluated as having high methodological quality, 7 had moderate methodological quality, and 4 had low methodological quality.⁵ Only 2 studies evaluated treatment for longer than 6 months.⁵ Outcomes for which there was low quality evidence are reported in **Table 2**; no outcomes were evaluated with moderate or high quality evidence. Outcomes were downgraded due to risk of publication bias and indirectness.⁵ Other comparisons and outcomes were graded as very low or insufficient quality.⁵ For this systematic review, clinical significance was predefined as a NNT or NNH of 10 or less compared to placebo, or for continuous outcomes, a standardized mean difference (SMD) of greater than 0.2 corresponding to a small effect size.⁵ SDM allows comparison of results between trials that use different scales and metrics to evaluate similar outcomes (e.g., pain relief). Generally, effects of treatment were modest and pain relief of more than 30% or 50% (NNT of 10 and 11, respectively) was largely balanced with drug intolerability (NNH 14).⁵ An older 2015 Cochrane review evaluated efficacy of milnacipran alone compared to placebo, included many of the same milnacipran studies (n=6), and found similar magnitude of benefit and harms for outcomes of 50% pain improvement, 30% pain improvement, and treatment withdrawal due to adverse events.¹⁹

Table 2. Outcomes for which there was low strength of evidence compared to placebo. Outcomes evaluating symptom improvement were generally self-reported.⁵

| Outcome | Interventions | Result | Authors Conclusions |
|-------------------------------------|---|---|----------------------------------|
| Efficacy Outcomes | | | |
| Pain relief of ≥50% | Duloxetine, milnacipran | 31% vs. 21%; ARR 0.09 (95% CI 0.07 to 0.11); NNT 11 | No clinically meaningful benefit |
| PGI-I of much or very much improved | Duloxetine, milnacipran | 51.9% vs. 29.3%; ARR 0.19 (95% CI 0.12 to 0.26); NNT 5 | Clinically meaningful benefit |
| Pain relief ≥30% | Duloxetine, milnacipran | 40.3% vs. 31.5%; ARR 0.10 (95% CI 0.08 to 0.12); NNT 10 | Clinically meaningful benefit |
| Pain intensity | Desvenlafaxine, duloxetine, milnacipran | SMD -0.22 (95% CI -0.27 to -0.17) | Clinically meaningful benefit |
| Tenderness | Duloxetine, milnacipran | SMD -0.21 (95% CI -0.33 to -0.09) | Clinically meaningful benefit |
| Disability | Duloxetine, milnacipran | SMD -0.21 (95% CI -0.26 to -0.16) | Clinically meaningful benefit |
| Quality of life | Duloxetine, milnacipran | SMD -0.20 (95% CI -0.25 to -0.15) | No clinically meaningful benefit |
| Fatigue | Desvenlafaxine, duloxetine, milnacipran | SMD -0.13 (95% CI -0.18 to -0.08) | No clinically meaningful benefit |
| Depression | Duloxetine, milnacipran | SMD -0.16 (95% CI -0.21 to -0.11) | No clinically meaningful benefit |

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|--|---|--|--------------------------------------|
| Cognitive disturbances | Duloxetine, milnacipran | SMD -0.16 (95% CI -0.21 to -0.10) | No clinically meaningful benefit |
| Discontinuation due to lack of benefit | Desvenlafaxine, duloxetine, milnacipran | 6.5% vs. 9.1%; ARR -0.03 (95% CI -0.04 to -0.02); NNT 33 | No clinically meaningful benefit |
| Sleep problems | Duloxetine, milnacipran | SMD -0.07 (95% CI -0.15 to 0.01) | No statistically significant benefit |
| Anxiety | Duloxetine, milnacipran | SMD -0.08 (95% CI -0.36 to 0.13) | No statistically significant benefit |
| Safety Outcomes | | | |
| Discontinuations due to AEs | Desvenlafaxine, duloxetine, milnacipran | 19.1% vs. 10.2%; ARR 0.07 (95% CI 0.04 to 0.10); NNH 14 | No clinically meaningful harm |
| Nausea | Desvenlafaxine, duloxetine, milnacipran | 32.0% vs. 14.2%; ARR 0.16 (95% CI 0.14 to 0.19); NNH 6 | Clinically meaningful harm |
| Somnolence | Duloxetine, milnacipran | 10.9% vs 4.7%; ARR 0.05 (95% CI 0.02 to 0.08); NNH 20 | No clinically meaningful harm |
| Insomnia | Desvenlafaxine, duloxetine, milnacipran | 9.6% vs. 5.8%; ARR 0.03 (95% CI 0.01 to 0.04); NNH 33 | No clinically meaningful harm |

Abbreviations: AE = adverse events; ARR = absolute risk reduction; CI = confidence interval; NNH = number needed to harm; NNT = number needed to treat; PGI-I = patient global impression of improvement; SMD = standardized mean difference

A 2018 Cochrane review evaluated the efficacy and safety of mirtazapine for treatment of fibromyalgia based on an analysis of 3 RCTs (n=606).²⁰ No outcomes were evaluated as moderate or high quality due to high risk of bias for included studies, indirectness, imprecision, and risk for publication bias.²⁰ There was low quality evidence of no difference compared to placebo for the following outcomes: 50% pain improvement and discontinuation due to adverse events.²⁰ Pain improvement of at least 30% was more common with mirtazapine compared to placebo (risk difference [RD] 0.13, 95% CI 0.05 to 0.21; NNT 8; low quality evidence).²⁰ Similar improvements were noted with participant-reported sleep problems (SMD -0.23, 95% CI -0.39 to -0.06, NNT 10; low quality evidence).²⁰ Adverse events which were more common with mirtazapine included somnolence (42% vs. 14%; RD 0.24, 95% CI 0.18 to 0.30; NNH 5; low quality evidence) and weight gain (19% vs. 1%; RD 0.17; 95% CI 0.11 to 0.23; NNH 6; low quality evidence).²⁰ Risks and benefits of therapy should be considered carefully as somnolence and weight gain were experienced frequently compared to the proportion of patients who achieved a moderate benefit from therapy.

A 2015 AHRQ systematic review examined the efficacy and safety of fibromyalgia treatments (pharmacological and non-pharmacological) in adult subgroups.⁹ The review included data from 34 RCTs and observational studies.⁹ All studies for pharmacological treatment had high risk of bias due to high attrition, reporting bias, small sample sizes, and source of funding.⁹ There was low strength of evidence of no difference in pain outcomes (PGI-I and BPI) with treatment of duloxetine in patients with depression or based on age compared to the general population.⁹ Similarly, there was no difference in PGI-I score with duloxetine treatment based on sex or race (low strength of evidence).⁹ Evidence for other outcomes or interventions of interest was of insufficient strength.⁹ Data were only available on short-term outcomes (3 months), and were limited by inconsistencies across studies and selective reporting of subgroup outcomes.⁹ For example, data on physical and social function were not commonly reported, and it is unclear if modest improvements in pain outcomes would be sustained over time.

A 2011 DERP systematic review evaluated direct comparative evidence for fibromyalgia treatments.²¹ Only 4 small RCTs were identified which compared amitriptyline to cyclobenzaprine, fluoxetine, nortriptyline, and immediate release paroxetine.²¹ There was no difference in any efficacy outcomes upon comparison of amitriptyline to cyclobenzaprine or nortriptyline (low strength evidence).²¹ Immediate release paroxetine 20 mg demonstrated a statistically significant improvement in pain (28% vs. 1%) and sleep problems (39% vs. 13%) compared to placebo over 6 weeks (low strength evidence based on 1 fair quality RCT of 68 patients).²¹ Evidence for the comparison of amitriptyline to fluoxetine was insufficient.²¹

Multiple systematic reviews, primarily Cochrane reviews, have been published assessing evidence for other pharmacotherapies for treatment of fibromyalgia. Pharmacotherapies studied include the following: monoamine oxidase inhibitors,²² selective serotonin reuptake inhibitors,²³ cannabinoids,²⁴ oral non-steroidal anti-inflammatory drugs,²⁵ antipsychotics,²⁶ amitriptyline,^{7,8} gabapentin,²⁷ topiramate,²⁸ lamotrigine,²⁹ oxycodone,³⁰ phenytoin,³¹ clonazepam,³² carbamazepine,³³ lacosamide,³⁴ valproic acid or valproate,³⁵ and antiepileptic drugs in children and adolescents.³⁶ An assessment of combination treatment for fibromyalgia included tramadol/acetaminophen, pregabalin/duloxetine, NSAIDs/benzodiazepines, amitriptyline/fluoxetine, amitriptyline/naproxen, amitriptyline/lidocaine, melatonin/antidepressant, carisoprodol/acetaminophen/caffeine, malic acid/magnesium, and MAOI/5-hydroxytryptophan.³⁷ Evidence from these reviews was generally of insufficient to very low quality for clinical outcomes of interest upon comparison to placebo or other therapies. Quality of evidence was limited by high or unclear risk of bias, limited population size, or small effect sizes. Estimates associated with the magnitude of benefit or risks associated with adverse effects for these therapies are extremely uncertain.

After review, 13 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), or outcome studied (e.g., non-clinical).³⁸⁻⁵⁰

Guidelines:

No guidelines met quality inclusion criteria. After review, 2 guidelines were excluded due to lack of methodological documentation¹⁵ or conflicts of interest.¹³

Randomized Controlled Trials:

A total of 311 citations were manually reviewed from the initial literature search. Only trials reporting new evidence were considered for inclusion, and trials which offered no new additional information from sources already in the review were excluded. Citations were also excluded because of wrong study design (eg, observational, post-hoc analysis), comparator (eg, no control), outcome studied (eg, non-clinical). The remaining 10 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 3. Description of Randomized Comparative Clinical Trials.

| Study/Design | Comparison | Population | Primary Outcome | Results |
|---|---|--|--|---|
| Allen, 2017 ⁵¹ MC, DB, PC RCT Duration: planned for 27 weeks; early study termination at 15 weeks N=697 | 1. Desvenlafaxine 50 mg 2. Desvenlafaxine 100mg 3. Desvenlafaxine 200 mg 4. Desvenlafaxine 400mg 5. Placebo | Adults with fibromyalgia and an average pain score ≥4 on the numeric rating scale (range 0-10) United States | Change from baseline in numeric rating scale pain score at study end (evaluated as a weekly mean score) | Change from baseline at week 15: 1. -2.09 points 2. -2.07 points 3. -2.24 points 4. -2.14 points 5. -2.21 points Early study termination due to lack of efficacy at week 15; treatment discontinuation: 68% of all patients, 28% due to early trial termination |
| Allen, 2017 ⁵¹ | 1. Desvenlafaxine 200 mg 2. Pregabalin 450 mg | Adults with fibromyalgia and an | Change from baseline in the | Change from baseline (mean, SE): 1. -1.60 (0.37) |

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| <p>MC, DB, PC, parallel-group, RCT</p> <p>1 week placebo run-in period and patients with >30% reduction in pain were excluded from the double-blind treatment phase</p> <p>Duration: 8 weeks N=125</p> | <p>3. Placebo</p> | <p>average pain score ≥ 4 on the numeric rating scale</p> <p>United States</p> | <p>numeric rating scale pain score at study end (evaluated as a weekly mean score)</p> | <p>2. -1.70 (0.38) 3. -1.98 (0.37)</p> <p>Early study termination for business reasons; treatment discontinuation: 49% of all patients, 29% due to early trial termination</p> |
| <p>Ang, 2013⁵²</p> <p>DB, RCT N=58 Duration: 21 weeks</p> | <p>1. Milnacipran 100 mg + CBT 2. Milnacipran 100 mg + education 3. Placebo + CBT</p> <p>Treatments given in combination with other baseline pharmacotherapy but not with formal physical or exercise therapy</p> | <p>Adults with fibromyalgia and weekly average pain intensity score ≥ 4, on stable medication for ≥ 4 weeks.</p> <p>United States</p> | <p>Change from baseline in the weekly average pain intensity (range 0-10) and physical function (SF-36 physical function scale; range 0-100)</p> | <p>Pain intensity 1. -2.15 (0.43) 2. -0.97 (0.43) 3. -1.67 (0.45) 1 vs. 2: MD -1.18 (0.62), p=0.07 1 vs. 3: MD -0.49 (0.62), p=0.44 2 vs. 3: MD 0.69 (0.64), p=0.28</p> <p>Physical function 1. 13.47 (3.74) 2. 4.05 (3.84) 3. 15.04 (4.01) 1 vs. 2: MD 9.42 (5.48), p=0.09 1 vs. 3: MD -1.58 (5.50), p=0.77 2 vs. 3: MD 11.0 (5.66), p=0.06</p> |
| <p>Arnold, 2015⁵³</p> <p>DB, MC, PC, cross-over, RCT</p> <p>Duration: 2 blinded 6-week periods separated by a 2 week taper and washout period</p> <p>N=197 randomized (318 screened)</p> | <p>1. Pregabalin 150-450 mg titrated based on efficacy and tolerability 2. Placebo</p> | <p>Adults with fibromyalgia and a pain intensity score ≥ 4 and comorbid depression on stable SSRI or SNRI treatment</p> <p>Spain, Italy, Canada, United States</p> | <p>Weekly average pain intensity score (range 0-10) at end of treatment</p> | <p>Pain intensity at week 6 * 1. 4.84 (0.15) 2. 5.45 (0.16) MD -0.52 (95% CI -0.62 to -0.41); p<0.0001</p> |
| <p>Holman, 2005⁵⁴</p> <p>Single-center, DB, PC, RCT N=60</p> | <p>1. Pramipexole 4.5mg 2. Placebo</p> | <p>Adults >21 years with fibromyalgia and pain scores ≥ 5</p> | <p>Improvement in pain score (VAS, range 0-10) at 14 weeks</p> | <p>Mean change in pain score (SE) at week 14 1. -2.48 (0.38) 2. -0.71 (0.54) MD -1.77 (95% CI -3.07 to 0.47); p=0.008</p> |

| | | | | |
|---|--|---|--|--|
| Duration: 14 weeks | Treatments given in combination with other baseline pharmacotherapy | United States | | |
| Luciano, 2014 ⁵⁵ OL, RCT N=156 Duration: 6 months | <ol style="list-style-type: none"> 1. Acceptance and commitment therapy 2. Pregabalin 300-600mg + duloxetine 60-120mg with comorbid depression 3. No treatment (waitlist) | <p>Adults with fibromyalgia</p> <p>Spain</p> | Fibromyalgia impact questionnaire (range 0-100) | <p>Mean change in the fibromyalgia impact questionnaire from baseline to 6 months</p> <ol style="list-style-type: none"> 1. -18.71 2. -3.85 3. 1.58 |
| Martin, 2014 ⁵⁶ Single center, OL, RCT N=180 Duration: 6 months | <ol style="list-style-type: none"> 1. Psychological (CBT), medical, educational and psysiotherapeutic interventions twice weekly 2. Pharmacological treatment with amitriptyline (max 75mg), acetaminophen (max 4000 mg, and tramadol (max 400 mg) | <p>Adults with fibromyalgia</p> <p>Spain</p> | Change in fibromyalgia impact questionnaire (range 0-100), pain in the last week, fatigue, anxiety, or coping mechanisms | <p>Mean fibromyalgia impact questionnaire at 6 months</p> <ol style="list-style-type: none"> 1. 70.33 (SD 16.48) 2. 76.81 (SD 14.18) <p>p=0.04</p> <p>No difference in other outcomes</p> <p>Attrition:</p> <ol style="list-style-type: none"> 1. 20 (22%) 2. 34 (37%) |
| Mease, 2013 ⁵⁷ OL, MC, RCT N=705 enrolled, 364 randomized, 264 completed study 4-12 week run-in period to evaluate response to pregabalin monotherapy; patients with incomplete response were randomized for 11 weeks | <ol style="list-style-type: none"> 1. Pregabalin 300-450 mg 2. Pregabalin 300-450 mg + milnacipran 100 mg | <p>Fibromyalgia with pain score >40 (0-100 VAS scale)</p> <p>United States</p> | PGIC responder defined as much or very much improved (score of 1 or 2 on a scale of 1-7) | <p>PGIC response</p> <ol style="list-style-type: none"> 1. 20.8% 2. 46.4% <p>MD 25.6%; P<0.001</p> |
| Moldofsky, 2011 ⁵⁸ DB, MC, PC, phase 2, RCT N=36 Duration: 8 weeks | <ol style="list-style-type: none"> 1. Cyclobenzaprine 1 mg to 4 mg titrated based on tolerability 2. Placebo | Adults with fibromyalgia and interrupted sleep for >50% of nights for 3 months before randomization | Fibromyalgia symptom improvement (use of LOCF for 7 patients who discontinued the study) | <p>Mean change in musculoskeletal pain (assessed with a 7 point scale a 10 body sites)</p> <ol style="list-style-type: none"> 1. -0.6 2. 0 <p>MD 0.6, p=0.044</p> |

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| | | Canada | | <p>Mean change in HAD depression subscale (range 0-21)</p> <ol style="list-style-type: none"> -1.4 0.7 <p>MD 2.1; p=0.023</p> <p>No significant differences in fatigue or total HAD score</p> |
| <p>Olivan-Blazquez, 2014⁵⁹</p> <p>DB, PC, RCT</p> <p>N=63</p> <p>Duration: 6 months</p> | <ol style="list-style-type: none"> Memantine 20 mg Placebo | <p>Adults with fibromyalgia</p> <p>Spain</p> | <p>Pain Improvement by VAS (range 0-10)</p> | <p>Mean (SD) VAS at 6 months (with imputation using LOCF for 17% of patients who discontinued the study)</p> <ol style="list-style-type: none"> 4.87 (1.45) 7.01 (1.53) <p>MD 2.14; p=0.001</p> |
| <p>Ramzy, 2017⁶⁰</p> <p>Single-center, RCT</p> <p>N=75</p> <p>Duration: 6 months</p> | <ol style="list-style-type: none"> Amitriptyline 25 mg daily Venlafaxine 75 mg daily Paroxetine 25 mg daily <p>Given in combination with pregabalin 75 mg daily</p> | <p>Adults with fibromyalgia</p> <p>Egypt</p> | <p>Somatic Symptoms Scale-8 (range 0-32)</p> | <p>Somatic Symptoms Scale-8 at 6 months (median, range)</p> <ol style="list-style-type: none"> 7 (0-14) 8 (8-8) 6 (4-13) <p>1 vs. 3: p<0.05 2 vs. 3: p<0.02</p> |
| <p>Russell, 2000⁶¹</p> <p>MC, DB, PC, discontinuation, RCT</p> <p>N=100 enrolled, 69 randomized</p> <p>Duration: 9 weeks</p> <p>All patients given open-label tramadol for 3 weeks and then patients with treatment benefit were blinded and randomized to placebo or tramadol for 6 weeks</p> | <ol style="list-style-type: none"> Tramadol (50-400 mg daily titrated based on tolerability during open-label phase) Placebo | <p>Adults with fibromyalgia</p> <p>United States</p> | <p>Time to treatment discontinuation due to inadequate pain relief</p> | <p>Time to treatment discontinuation graphically reported ; p=0.001</p> <p>Proportion of patients who maintained treatment at 6 weeks</p> <ol style="list-style-type: none"> 20 (57.1% of randomized patients; 20% of enrolled patients) 9 (27% of randomized patients; 9% of enrolled patients) <p>MD 30.1%; p=0.015</p> <p>Discontinuation due to adverse events (primarily nausea, vomiting, dizziness): n= 20 (20% of enrolled patients receiving tramadol)</p> |

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; DB = double blind; HAD = hospital anxiety and depression scale; LOCF = last observation carried forward; MC = multicenter; MD = mean difference; OL = open label; PC = placebo-controlled; PGIC = patient global impression of change scale; RCT = randomized clinical trial; SC = single-center; SD = standard deviation; SE = standard error; VAS = visual analog scale.

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54. Holman AJ, Myers RR. A randomized, double-blind, placebo-controlled trial of pramipexole, a dopamine agonist, in patients with fibromyalgia receiving concomitant medications. *Arthritis and rheumatism*. 2005;52(8):2495-2505.
55. Luciano JV, Guallar JA, Aguado J, et al. Effectiveness of group acceptance and commitment therapy for fibromyalgia: a 6-month randomized controlled trial (EFFIGACT study). *Pain*. 2014;155(4):693-702.
56. Martin J, Torre F, Aguirre U, et al. Evaluation of the interdisciplinary PSYMEPHY treatment on patients with fibromyalgia: a randomized control trial. *Pain medicine (Malden, Mass)*. 2014;15(4):682-691.
57. Mease PJ, Farmer MV, Palmer RH, et al. Milnacipran combined with pregabalin in fibromyalgia: a randomized, open-label study evaluating the safety and efficacy of adding milnacipran in patients with incomplete response to pregabalin. *Ther Adv Musculoskelet Dis*. 2013;5(3):113-126.
58. Moldofsky H, Harris HW, Archambault WT, et al. Effects of bedtime very low dose cyclobenzaprine on symptoms and sleep physiology in patients with fibromyalgia syndrome: a double-blind randomized placebo-controlled study. *The Journal of rheumatology*. 2011;38(12):2653-2663.
59. Olivan-Blazquez B, Herrera-Mercadal P, Puebla-Guedea M, et al. Efficacy of memantine in the treatment of fibromyalgia: A double-blind, randomised, controlled trial with 6-month follow-up. *Pain*. 2014;155(12):2517-2525.
60. Ramzy EA. Comparative Efficacy of Newer Antidepressants in Combination with Pregabalin for Fibromyalgia Syndrome: A Controlled, Randomized Study. *Pain practice : the official journal of World Institute of Pain*. 2017;17(1):32-40.

61. Russell IJ, Kamin M, Bennett RM, et al. Efficacy of tramadol in treatment of pain in fibromyalgia. *Journal of clinical rheumatology : practical reports on rheumatic & musculoskeletal diseases*. 2000;6(5):250-257.
62. Cymbalta (duloxetine delayed release capsules) [package insert] Indianapolis, IN: Eli Lilly and Company; 2017.
63. Savella (milnacipran HCl tablets) [package insert] Irvine, CA: Allergan USA, Inc.; 2017.

Appendix 1: Specific Drug Information for FDA-approved drugs

Table A1. Clinical Pharmacology and Pharmacokinetics.¹⁰⁻¹²

| Drug Name | Mechanism of Action | Absorption | Metabolism/Excretion | Pharmacokinetics (mean) |
|-------------|--|---|---|--|
| Duloxetine | Serotonin and norepinephrine reuptake inhibitor | Well absorbed | Hepatic metabolism via CYP1A2 and CYP2D6 Excreted in urine (70%) and feces (20%) | <ul style="list-style-type: none"> • Half-life: 12 hours • Cmax: 6 hours • Vd: 1640 L (>90% protein binding) |
| Milnacipran | Serotonin and norepinephrine reuptake inhibitor | Well absorbed Bioavailability 85-90% | Hepatic metabolism Urinary excretion (50% as unchanged drug) | <ul style="list-style-type: none"> • Half-life: 6-8 hours • Cmax: 2-4 hours • Vd: 400 L (13% protein binding) |
| Pregabalin | Binds voltage-gated calcium channels, modulates calcium influx in nerves, and inhibits neurotransmitter release including glutamate, norepinephrine, serotonin, dopamine, substance P, and calcitonin gene-related peptide | Bioavailability 90% | Excreted unchanged in urine (90%) | <ul style="list-style-type: none"> • Half-life: 6 hours for adults • Cmax: ER 8 hours, IR 3 hours • Vd: 0.5 L/kg (0% protein binding) |

Use in Specific Populations:

Duloxetine:⁶²

Pregnancy: Based on animal data, may cause fetal harm.

Lactation: Exercise caution when administering to a nursing woman.

Hepatic impairment: Avoid use in patients with chronic liver disease or cirrhosis.

Renal impairment: Avoid use in patients with severe renal impairment (eGFR <30 mL/min).

Geriatric use: Falls and clinically significant hyponatremia have been reported. No dose adjustment recommended based on age.

Smoking Status: Bioavailability of duloxetine is reduced with concomitant smoking, but dose adjustments are not recommended.

Milnacipran:⁶³

Pregnancy: Based on animal data, may cause fetal harm.

Lactation: Milnacipran is present in milk, and there is limited data regarding infant exposure. Use caution if administered while breastfeeding.

Hepatic impairment: Avoid use in patients with chronic liver disease or cirrhosis.

Renal impairment: Used with caution in patients with moderate renal impairment.

Geriatric use: Clinically significant hyponatremia have been reported in elderly patients; consider discontinuation if present.

Pediatric use: Safety and effectiveness in pediatric patients with fibromyalgia has not been established. Use in pediatric patients is not recommended.

Pregabalin:¹⁶

Pregnancy: May cause fetal harm. Advise of potential risks to the fetus.

Lactation: Breastfeeding is not recommended due to potential risk of tumorigenicity.

Renal impairment: Dose adjustment recommended for those with renal impairment.

Pediatric use: Safety and effectiveness in pediatric patients with fibromyalgia has not been established.

Drug Safety:

Boxed Warnings:^{62,63}

- Duloxetine: Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants. Monitor for worsening and emergence of suicidal thoughts and behaviors.
- Milnacipran (Savella®): Increased risk of suicidal ideation, thinking, and behavior in children, adolescents, and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders. Savella® is not approved for use in pediatric patients.

Contraindications:

- Duloxetine and milnacipran– Serotonin syndrome and monoamine oxidase inhibitors.^{62,63}
Do not use MAOIs intended to treat psychiatric disorders with duloxetine or within 5 days of stopping treatment with duloxetine. Do not use duloxetine within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start duloxetine in a patient who is being treated with linezolid or intravenous methylene blue.
- Pregabalin – Known hypersensitivity to pregabalin.¹⁶

Table A2. Summary of Warnings and Precautions.^{16,62,63}

| Warning/Precaution | Duloxetine | Milnacipran | Pregabalin |
|--|------------|-------------|------------|
| Suicidal thoughts/risk | X | X | X |
| Seizures | X | X | X |
| Serotonin syndrome | X | X | |
| Hepatotoxicity | X | X | |
| Abnormal bleeding | X | X | |
| Withdrawal symptoms upon discontinuation | X | X | |
| Urinary hesitation and retention | X | X | |
| Increased blood pressure and heart rate | X | X | |
| Orthostatic Hypotension, falls and syncope | X | | |
| Dizziness and somnolence | | | X |
| Activation of mania or hypomania | X | X | |
| Angle-closure glaucoma | X | X | |
| Hyponatremia | X | X | |
| Drug interactions with inhibitors of CYP1A2 and thioridazine | X | | |
| Worsening glucose control in diabetes | X | | |

| | | | |
|---|---|--|---|
| Conditions that slow gastric emptying | X | | |
| Severe skin reactions | X | | |
| Peripheral edema | | | X |
| Hypersensitivity reactions and angioedema | | | X |
| Weight gain | | | X |
| Tumorigenic potential | | | X |
| Ophthalmologic effects | | | X |
| Creatine Kinase Elevations | | | X |
| Decreased platelet count | | | X |
| PR interval prolongation | | | X |

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) 1946 to October Week 1 2018

| | | |
|----|--|--------|
| 1 | exp Analgesics, Opioid/ | 105716 |
| 2 | exp Anti-Inflammatory Agents, Non-Steroidal/ | 186834 |
| 3 | exp Antidepressive Agents/ | 136270 |
| 4 | exp Anticonvulsants/ | 132011 |
| 5 | gabapentin.mp. | 5351 |
| 6 | topiramate.mp. | 4007 |
| 7 | lacosamide.mp. | 582 |
| 8 | exp Benzodiazepines/ | 63145 |
| 9 | exp Cannabinoids/ | 12538 |
| 10 | nabilone.mp. | 265 |
| 11 | exp Amantadine/ | 5626 |
| 12 | milnacipran.mp. | 596 |
| 13 | pramipexole.mp. | 1245 |
| 14 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 | 593078 |
| 15 | exp Fibromyalgia/ | 7773 |
| 16 | 14 and 15 | 868 |
| 17 | limit 16 to (english language and humans) | 736 |
| 18 | limit 17 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews) | 311 |

Appendix 3. Abstracts of randomized controlled trials

1. Allen R, Sharma U, Barlas S. Clinical Experience With Desvenlafaxine in Treatment of Patients With Fibromyalgia Syndrome. *Clinical pharmacology in drug development*. 2017;6(3):224-233.
Two multicenter, randomized, placebo-controlled, adaptive-design trials of desvenlafaxine for fibromyalgia syndrome (FMS) were conducted. In study 1, male and female patients were randomized to a 27-week treatment with placebo or desvenlafaxine 50, 100, 200, or 400 mg/d. In study 2, female patients were randomized to an 8-week treatment with placebo, desvenlafaxine 200 mg/d, or pregabalin 450 mg/d after a placebo run-in. The primary efficacy end point was change from baseline in numeric rating scale (NRS) pain score. Protocol-specified interim analyses were planned after 12 (study 1) and 8 (study 2) weeks of treatment. Safety data were collected. In all, 697 patients were randomly assigned to treatment in study 1. At the interim analysis (n = 346), none of the desvenlafaxine doses met the efficacy criteria (mean [SE] advantage over placebo, -0.21 [0.36] to 0.04 [0.35]), and the study was terminated. Study 2 was stopped for business reasons before the planned interim analysis. NRS scores in week 8 were -1.98 (0.37), -1.60 (0.37), and -1.70 (0.38) for placebo (n = 26), desvenlafaxine 250 mg/d (n = 24), and pregabalin 450 mg/d (n = 21), respectively; neither active treatment differed significantly from placebo. Desvenlafaxine was generally safe and well tolerated. Efficacy of desvenlafaxine for pain associated with FMS was not demonstrated.
2. Ang DC, Jensen MP, Steiner JL, et al. Combining cognitive-behavioral therapy and milnacipran for fibromyalgia: a feasibility randomized-controlled trial. *The Clinical journal of pain*. 2013;29(9):747-754.
OBJECTIVES: To evaluate the feasibility of a randomized-controlled trial and to obtain estimates of the effects of combined cognitive-behavioral therapy (CBT) and milnacipran for the treatment of fibromyalgia., METHODS: Fifty-eight patients with fibromyalgia were randomized to 1 of the 3 treatment arms: (1) combination therapy (n = 20); (2) milnacipran+education (n = 19); and (3) placebo+CBT (n = 19). Patients received either milnacipran (100 mg/d) or placebo. Patients also received 8 sessions of phone-delivered CBT or educational instructions, but only from baseline to week 9. Assessments were conducted at baseline, week 9, and 21. The primary endpoints were baseline to week 21 changes in weekly average pain intensity and physical function (SF-36 physical function scale)., RESULTS: Compared with milnacipran, combination therapy demonstrated a moderate effect on improving SF-36 physical function (SE = 9.42 [5.48], P = 0.09, effect size = 0.60) and in reducing weekly average pain intensity (mean difference [SE] = -1.18 [0.62], P = 0.07, effect size = 0.67). Compared with milnacipran, CBT had a moderate to large effect in improving SF-36 physical function (mean difference [SE] = 11.0 [5.66], P = 0.06, effect size = 0.70). Despite the presence of concomitant centrally acting therapies, dropout rate was lower than anticipated (15% at week 21). Importantly, at least 6 out of the 8 phone-based therapy sessions were successfully completed by 89% of the patients; and adherence to the treatment protocols was > 95%. CONCLUSIONS: In this pilot study, a therapeutic approach that combines phone-based CBT and milnacipran was feasible and acceptable. Moreover, the preliminary data supports conducting a fully powered randomized-controlled trial.
3. Arnold LM, Sarzi-Puttini P, Arsenault P, et al. Efficacy and Safety of Pregabalin in Patients with Fibromyalgia and Comorbid Depression Taking Concurrent Antidepressant Medication: A Randomized, Placebo-controlled Study. *The Journal of rheumatology*. 2015;42(7):1237-1244.
OBJECTIVE: To assess pregabalin efficacy and safety in patients with fibromyalgia (FM) with comorbid depression taking concurrent antidepressant medication., METHODS: This randomized, placebo-controlled, double-blind, 2-period, 2-way crossover study was composed of two 6-week treatment periods separated by a 2-week taper/washout phase. Patients with FM (aged ≥ 18 yrs) taking a stable dose of a selective serotonin reuptake inhibitor (SSRI) or a serotonin/norepinephrine reuptake inhibitor (SNRI) for depression were randomized 1:1 to receive pregabalin/placebo or placebo/pregabalin (optimized to 300 or 450 mg/day). Antidepressant medication was continued throughout the study. The primary efficacy outcome was the mean pain score on an 11-point numerical rating scale. Secondary efficacy outcomes included measures of anxiety, depression, patient function, and sleep., RESULTS: Of 197 patients randomized to treatment, 181 and 177 received ≥ 1 dose of pregabalin and placebo, respectively. At baseline, 52.3% of patients were taking an SSRI and 47.7% an SNRI, and mean pain score was 6.7. Mean pain scores at endpoint were statistically significantly reduced with pregabalin (least squares mean difference from placebo -0.61, 95% CI -0.91 - -0.31, p = 0.0001). Pregabalin significantly improved Hospital Anxiety and Depression Scale-Anxiety (difference -0.95, p < 0.0001) and -Depression (difference -0.88, p = 0.0005) scores, Fibromyalgia Impact Questionnaire total score (difference -6.60, p < 0.0001), and sleep quality (difference 0.57, p < 0.0001), but not EuroQol 5-Dimensions score (difference 0.02, p = 0.3854). Pregabalin safety was consistent with previous studies and current product labeling., CONCLUSION: Compared with placebo, pregabalin statistically significantly improved FM pain and other symptoms in patients taking antidepressant medication for comorbid depression. ClinicalTrials.gov identifier: NCT01432236.

4. Holman AJ, Myers RR. A randomized, double-blind, placebo-controlled trial of pramipexole, a dopamine agonist, in patients with fibromyalgia receiving concomitant medications. *Arthritis and rheumatism*. 2005;52(8):2495-2505.

OBJECTIVE: To assess the efficacy and safety of pramipexole, a dopamine 3 receptor agonist, in patients with fibromyalgia., METHODS: In this 14-week, single-center, double-blind, placebo-controlled, parallel-group, escalating-dose trial, 60 patients with fibromyalgia were randomized 2:1 (pramipexole:placebo) to receive 4.5 mg of pramipexole or placebo orally every evening. The primary outcome was improvement in the pain score (10-cm visual analog scale [VAS]) at 14 weeks. Secondary outcome measures were the Fibromyalgia Impact Questionnaire (FIQ), the Multidimensional Health Assessment Questionnaire (MDHAQ), the pain improvement scale, the tender point score, the 17-question Hamilton Depression Inventory (HAM-d), and the Beck Anxiety Index (BAI). Patients with comorbidities and disability were not excluded. Stable dosages of concomitant medications, including analgesics, were allowed., RESULTS: Compared with the placebo group, patients receiving pramipexole experienced gradual and more significant improvement in measures of pain, fatigue, function, and global status. At 14 weeks, the VAS pain score decreased 36% in the pramipexole arm and 9% in the placebo arm (treatment difference -1.77 cm). Forty-two percent of patients receiving pramipexole and 14% of those receiving placebo achieved > or =50% decrease in pain. Secondary outcomes favoring pramipexole over placebo included the total FIQ score (treatment difference -9.57) and the percentages of improvement in function (22% versus 0%), fatigue (29% versus 7%), and global (38% versus 3%) scores on the MDHAQ. Compared with baseline, some outcomes showed a better trend for pramipexole treatment than for placebo, but failed to reach statistical significance, including improvement in the tender point score (51% versus 36%) and decreases in the MDHAQ psychiatric score (37% versus 28%), the BAI score (39% versus 27%), and the HAM-d score (29% versus 9%). No end points showed a better trend for the placebo arm. The most common adverse events associated with pramipexole were transient anxiety and weight loss. No patient withdrew from the study because of inefficacy or an adverse event related to pramipexole., CONCLUSION: In a subset of patients with fibromyalgia, approximately 50% of whom required narcotic analgesia and/or were disabled, treatment with pramipexole improved scores on assessments of pain, fatigue, function, and global status, and was safe and well-tolerated.

5. Luciano JV, Guallar JA, Aguado J, et al. Effectiveness of group acceptance and commitment therapy for fibromyalgia: a 6-month randomized controlled trial (EFFIGACT study). *Pain*. 2014;155(4):693-702.

In the last decade, there has been burgeoning interest in the effectiveness of third-generation psychological therapies for managing fibromyalgia (FM) symptoms. The present study examined the effectiveness of acceptance and commitment therapy (ACT) on functional status as well as the role of pain acceptance as a mediator of treatment outcomes in FM patients. A total of 156 patients with FM were enrolled at primary health care centers in Zaragoza, Spain. The patients were randomly assigned to a group-based form of ACT (GACT), recommended pharmacological treatment (RPT; pregabalin + duloxetine), or wait list (WL). The primary end point was functional status (measured with the Fibromyalgia Impact Questionnaire, FIQ). Secondary end points included pain catastrophizing, pain acceptance, pain, anxiety, depression, and health-related quality of life. The differences between groups were calculated by linear mixed-effects (intention-to-treat approach) and mediational models through path analyses. Overall, GACT was statistically superior to both RPT and WL immediately after treatment, and improvements were maintained at 6 months with medium effect sizes in most cases. Immediately after treatment, the number needed to treat for 20% improvement compared to RPT was 2 (95% confidence interval 1.2-2.0), for 50% improvement 46, and for achieving a status of no worse than mild impaired function (FIQ total score <39) also 46. Unexpectedly, 4 of the 5 tested path analyses did not show a mediation effect. Changes in pain acceptance only mediated the relationship between study condition and health-related quality of life. These findings are discussed in relation to previous psychological research on FM treatment.

6. Martin J, Torre F, Aguirre U, et al. Evaluation of the interdisciplinary PSYMEPHY treatment on patients with fibromyalgia: a randomized control trial. *Pain medicine (Malden, Mass)*. 2014;15(4):682-691.

OBJECTIVE: Fibromyalgia (FM) is a chronic disorder that can have a devastating effect on patients' lives. This study assessed the efficacy of a 6-week interdisciplinary treatment that combines coordinated PSYchological, Medical, Educational, and PHYsiotherapeutic interventions (PSYMEPHY) compared with standard pharmacologic care., DESIGN: The study was a randomized controlled trial (54 participants in the PSYMEPHY group and 56 in the control group [CG]) with follow-up at 6 months. PSYMEPHY patients were also assessed at 12 months. The main outcomes were changes in total Fibromyalgia Impact Questionnaire (FIQ) score, pain, fatigue, morning tiredness, anxiety, and use of pain coping strategies as measured by the FIQ, the visual analog scale, and the Coping with Chronic Pain Questionnaire. After the 6-month assessment, patients in the CG were offered the PSYMEPHY treatment, and completed all of the instruments immediately after treatment, and at 6- and 12-month follow-up visits (N=93)., SETTING: Subjects received therapy at two different outpatient clinical locations., PATIENTS: Fibromyalgia patients., RESULTS: Six months after the intervention, significant improvements in total FIQ score (P=0.04), and pain (P=0.03) were seen in the PSYMEPHY group compared with controls. Twelve months after the intervention, all patients in the PSYMEPHY group maintained statistically significant improvements in total FIQ score, and pain, and showed an improvement in

fatigue, rested, anxiety, and current pain compared with baseline. Data from the control patients who underwent the PSYMEPHY intervention corroborated the initial results, CONCLUSIONS: This study highlights the beneficial effects of an interdisciplinary treatment for FM patients in a hospital pain management unit. A 6-week interdisciplinary intervention showed significant improvement in key domains of fibromyalgia, as quality of life, pain, fatigue, rested, and anxiety at 12 months.

7. Mease PJ, Farmer MV, Palmer RH, et al. Milnacipran combined with pregabalin in fibromyalgia: a randomized, open-label study evaluating the safety and efficacy of adding milnacipran in patients with incomplete response to pregabalin. *Ther Adv Musculoskelet Dis.* 2013;5(3):113-126.
OBJECTIVE: To evaluate the safety, tolerability, and efficacy of adding milnacipran to pregabalin in patients with fibromyalgia who have experienced an incomplete response to pregabalin. METHODS: In this randomized, multicenter, open-label study, patients received pregabalin 300 or 450 mg/day during a 4- to 12-week run-in period. Patients with weekly recall visual analog scale (VAS) pain score of at least 40 and up to 90, Patient Global Impression of Severity score of at least 4, and Patient Global Impression of Change (PGIC) score of at least 3 were classified as incomplete responders and randomized to continue pregabalin alone (n = 180) or receive milnacipran 100 mg/day added to pregabalin (n = 184). The primary efficacy parameter was responder status based on PGIC score of up to 2. The secondary efficacy parameter was change from randomization in weekly recall VAS pain score. Safety parameters included adverse events (AEs), vital signs, and clinical laboratory tests. RESULTS: The percentage of PGIC responders was significantly higher with milnacipran added to pregabalin (46.4%) than with pregabalin alone (20.8%; p < 0.001). Mean improvement from randomization in weekly recall VAS pain scores was greater in patients receiving milnacipran added to pregabalin (-20.77) than in patients receiving pregabalin alone (-6.43; p < 0.001). During the run-in period, the most common treatment-emergent AEs with pregabalin were dizziness (22.8%), somnolence (17.3%), and fatigue (9.1%). During the randomized period, the most common treatment-emergent AEs with milnacipran added to pregabalin were nausea (12.5%), fatigue (10.3%), and constipation (9.8%). CONCLUSIONS: In this exploratory, open-label study, adding milnacipran to pregabalin improved global status, pain, and other symptoms in patients with fibromyalgia with an incomplete response to pregabalin treatment.
8. Moldofsky H, Harris HW, Archambault WT, et al. Effects of bedtime very low dose cyclobenzaprine on symptoms and sleep physiology in patients with fibromyalgia syndrome: a double-blind randomized placebo-controlled study. *The Journal of rheumatology.* 2011;38(12):2653-2663.
OBJECTIVE: To determine the effects of bedtime very low dose (VLD) cyclobenzaprine (CBP) on symptoms and sleep physiology of patients with fibromyalgia (FM), unrefreshing sleep, and the alpha-nonREM sleep electroencephalographic (EEG) anomaly at screening., METHODS: Of 37 patients with FM in the screened population, 36 were randomized and treated in this 8-week, double-blind, placebo-controlled, dose-escalating study of VLD CBP 1-4 mg at bedtime. We evaluated changes in subjective symptoms including pain, tenderness, fatigue, mood [Hospital Anxiety and Depression Scale (HAD)], and objective EEG sleep physiology (at screening, baseline, and Weeks 2, 4, and 8)., RESULTS: In the VLD CBP-treated group (n = 18) over 8 weeks, musculoskeletal pain and fatigue decreased, tenderness improved; total HAD score and the HAD depression subscore decreased; patient-rated and clinician-rated fatigue improved. In the placebo-treated group (n = 18), none of these outcome measures changed significantly. Compared to placebo at 8 weeks, VLD CBP significantly improved pain, tenderness, and the HAD Depression subscore. Analysis of cyclic alternating pattern (CAP) sleep EEG revealed that significantly more subjects in the VLD CBP group than the placebo group had increased nights of restorative sleep in which $CAP(A2+A3)/CAP(A1+A2+A3) = CAP(A2+A3(Norm)) \leq 33\%$. For VLD CBP-treated subjects, the increase in nights with $CAP(A2+A3(Norm)) \leq 33\%$ was correlated to improvements in fatigue, total HAD score, and HAD depression score., CONCLUSION: Bedtime VLD CBP treatment improved core FM symptoms. Nights with $CAP(A2+A3(Norm)) \leq 33\%$ may provide a biomarker for assessing treatment effects on nonrestorative sleep and associated fatigue and mood symptoms in persons with FM.
9. Oliván-Blázquez B, Herrera-Mercadal P, Puebla-Guedea M, et al. Efficacy of memantine in the treatment of fibromyalgia: A double-blind, randomised, controlled trial with 6-month follow-up. *Pain.* 2014;155(12):2517-2525.
Fibromyalgia (FM) is a prevalent and disabling chronic disease. Recent studies have found elevated levels of glutamate in several brain regions, leading to hypotheses about the usefulness of glutamate-blocking drugs such as memantine in the treatment of FM. The aim of this study was to evaluate the efficacy of memantine in the treatment of pain and other clinical variables (global function, clinical impression, depression, anxiety, quality of life) in FM patients. A double-blind, parallel randomised controlled trial was developed. A total of 63 patients diagnosed with FM were recruited from primary health care centres in Zaragoza, Spain. Memantine was administered at doses of 20mg/d after 1 month of titration. Assessments were carried out at baseline, posttreatment, and 3- and 6-month follow-up. Compared with a placebo group, memantine significantly decreased ratings on a pain visual analogue scale (Cohen's d=1.43 at 6 months) and pain measured with a sphygmomanometer (d=1.05). All other secondary outcomes except anxiety also improved, with moderate-to-large effect sizes at 6 months. Compared with placebo, the absolute risk reduction obtained with memantine was 16.13% (95% confidence interval=2.0% to 32.6%), and the number needed to treat was 6.2 (95% confidence interval=3 to 47).

Tolerance was good, with dizziness (8 patients) and headache (4 patients) being the most frequent side effects of memantine. Although additional studies with larger sample sizes and longer follow-up times are needed, this study provides preliminary evidence of the utility of memantine for the treatment of FM.

10. Ramzy EA. Comparative Efficacy of Newer Antidepressants in Combination with Pregabalin for Fibromyalgia Syndrome: A Controlled, Randomized Study. *Pain practice : the official journal of World Institute of Pain*. 2017;17(1):32-40.

BACKGROUND: This controlled, randomized study investigated the hypothesis that the combined use of pregabalin plus paroxetine for fibromyalgia management would be associated with comparable Somatic Symptoms Scale-8 (SSS-8) and Center for Epidemiological Studies Depression Scale (CESDS) scores, but higher tolerability than the combined use of pregabalin plus either amitriptyline or venlafaxine., **METHODS:** After institutional ethics committee approval, 75 female subjects diagnosed with fibromyalgia and in receipt of pregabalin (75 mg/day) were randomly allocated to concurrently receive amitriptyline (25 mg/day; n = 24), venlafaxine (75 mg/day; n = 25), or paroxetine (25 mg/day; n = 26). All patients were assessed bimonthly for 6 consecutive months for changes in SSS-8 and CESDS scores, life satisfaction, mood, sleep quality, fatigue, medication tolerability, and adverse events., **RESULTS:** Compared with pregabalin plus amitriptyline or venlafaxine, the combined use of pregabalin plus paroxetine in fibromyalgia patients resulted in significantly lower SSS-8 and CESDS scores from 18 (P < 0.05) and 10 weeks (P < 0.001) after the initiation of study medications, respectively; higher medication tolerability (P < 0.001); improved life satisfaction, mood, and sleep quality at most observation times (P < 0.05); and fewer instances of dry mouth and elevated blood pressure (P < 0.02). Medication termination due to poor tolerability was observed most frequently in the venlafaxine group (P < 0.05), while drowsiness, dizziness, blurred vision, abnormal taste, hunger, hallucination, urination problems, and sexual dysfunction were observed most frequently in the amitriptyline group (P < 0.02)., **CONCLUSION:** The combined use of pregabalin plus paroxetine offers an effective method with increased tolerability to reduce the somatic and depressive symptoms of fibromyalgia and to enhance the quality of life in affected individuals.

Appendix 4: Key Inclusion Criteria

| | |
|---------------------|--|
| Population | Patients with fibromyalgia |
| Intervention | Antidepressant, antiepileptic, or analgesic pharmacotherapy |
| Comparator | Placebo, other pharmacotherapy, or non-pharmacological therapy |
| Outcomes | Symptom improvement Functional improvement Quality of life Morbidity Mortality Severe adverse events Discontinuation due to adverse events |
| Setting | Outpatient |

Pregabalin

Goal(s):

- Provide coverage only for funded diagnoses that are supported by the medical literature.

Length of Authorization:

- 90 days to lifetime (criteria-specific)

Requires PA:

- Pregabalin and pregabalin extended release

Covered Alternatives

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

| Approval Criteria | | |
|---|---|----------------------|
| 1. Is this a request for renewal of a previously approved prior authorization for pregabalin? | Yes: Go to Renewal Criteria | No: Go to # 2 |
| 2. What diagnosis is being treated? | Record ICD10 code | |
| 3. Is the request for pregabalin immediate release? | Yes: Go to #4 | No: Go to #5 |
| 4. Does the patient have a diagnosis of epilepsy? | Yes: Approve for lifetime | No: Go to #5 |

| Approval Criteria | | |
|--|---------------------------------|--|
| 5. Is the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (see Table 1 below for examples)? | Yes: Go to #6 | No: Pass to RPh. Deny; not funded by the OHP. |
| 6. Has the patient tried and failed gabapentin therapy for 90 days or have contradictions or intolerance to gabapentin? | Yes: Approve for 90 days | No: Pass to RPh. Deny and recommend trial of gabapentin for 90 days |

| Renewal Criteria | | |
|--|---|--|
| 1. Does the patient have documented improvement from pregabalin? | Yes: Approve for up to 12 months | No: Pass to RPh. Deny for medical appropriateness |

Table 1. OHP Funded Diagnosis and Evidence Supports Drug Use in Specific Indication

| Condition | Pregabalin | Pregabalin Extended-Release |
|---------------------------------|------------|-----------------------------|
| Funded | | |
| Diabetic Neuropathy | X | X |
| Postherpetic Neuropathy | X | X |
| Painful Polyneuropathy | X | |
| Spinal Cord Injury Pain | X | |
| Chemotherapy Induced Neuropathy | X | |

| | | |
|--------------|---|--|
| Non-funded | | |
| Fibromyalgia | X | |

P&T Review: 7/18 (DM); 3/18; 3/17
Implementation: 8/15/18; 4/1/17

Milnacipran

Goal(s):

- Provide coverage only for funded diagnoses that are supported by the medical literature.

Length of Authorization:

- 90 days

Requires PA:

- Milnacipran

Covered Alternatives

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

| Approval Criteria | | |
|---|---------------------------------|-----------------------------------|
| 1. What diagnosis is being treated? | Record ICD10 code | |
| 2. Is the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (see Table 1 below for examples)? | Yes: Approve for 90 days | No: Go to #3. Pass to RPh. |
| 3. Pass to RPh. The prescriber must provide documentation of therapeutic failure, adverse event, or contraindication alternative drugs approved by FDA for the funded condition. The prescriber must provide medical literature supporting use for the funded condition. RPh may use clinical judgement to approve drug for up to 6 months or deny request based on documentation provided by prescriber. | | |

Table 1. OHP Funded or Non-Funded Diagnosis and Evidence Supports Drug Use in Specific Indication

| Condition | Milnacipran |
|---------------------------------|--------------------|
| Funded | |
| Diabetic Neuropathy | |
| Postherpetic Neuropathy | |
| Painful Polyneuropathy | |
| Spinal Cord Injury Pain | |
| Chemotherapy Induced Neuropathy | |
| Non-funded | |
| Fibromyalgia | X |

P&T Review: 7/18 (DM); 3/17

Implementation: 4/1/17

Hidradenitis Suppurativa

Question: Should hidradenitis suppurativa be moved to a higher priority line on the Prioritized List?

Question source: John Young, MD and LaDessa Christensen NP-C, Silver Falls Dermatology; Jill Moore, MD, Phoebe Rich Dermatology; Julie Dhossche, MD and Tracy Funk, MD, OHSU Dermatology

Issue: Hidradenitis suppurativa (HS) (ICD-10 L73.2) is currently on line 512 HIDRADENITIS SUPPURATIVA; DISSECTING CELLULITIS OF THE SCALP. Multiple dermatology providers are requesting that it be considered for a covered line on the List based on the development of newer, more effective treatments for this condition, specifically adalimumab (Humira). Adalimumab was approved for treatment of hidradenitis suppurativa by the FDA in 2015. It was not considered in the most recent review of this condition, the 2012 ICD-10 Dermatology review. During the 2012 review, no effective treatments were found for HS, and therefore the condition was placed on a low priority line. Adalimumab is an antibody that inhibits tumor necrosis factor (TNF). It is given by subcutaneous injection. Other biologic medications such as infliximab and etanercept are being used to treat HS, although neither has FDA approval for treating HS. HS is considered a similar condition to acne conglobata, which was moved to a covered line with the 2012 ICD-10 Dermatology review.

Background:

Hidradenitis suppurativa (HS) is a chronic inflammatory skin condition characterized by recurrent painful boils in flexural sites, such as the axillae and groin, that affects about 1% of the population, with onset in early adulthood. The exact cause is unclear but believed to involve a combination of genetic and environmental factors. Diagnosis is based on the symptoms. There is no known cure. Warm baths may be tried in those with mild disease. Cutting open the lesions to allow them to drain does not result in significant benefit. While antibiotics are commonly used, evidence for their use is poor. Immunosuppressive medication may also be tried. In those with more severe disease laser therapy or surgery to remove the affected skin may be carried out.

Hurley's staging system:

| Stage | Characteristics |
|--------------|---|
| I | Solitary or multiple isolated abscess formation without scarring or sinus tracts (A few minor sites with rare inflammation; may be mistaken for acne.) |
| II | Recurrent abscesses, single or multiple widely separated lesions, with sinus tract formation. (Frequent inflammation restrict movement and may require minor surgery such as incision and drainage.) |
| III | Diffuse or broad involvement across a regional area with multiple interconnected sinus tracts and abscesses (Inflammation of sites to the size of golf balls, or sometimes baseballs; scarring develops, including subcutaneous tracts of infection. Patients at this stage may be unable to function.) |

Sartorius staging system

- Anatomic regions involved (axilla, groin gluteal, or other region or inframammary region left or right)
- Number and types of lesions involved (abscesses, nodules, fistulas [actually sinuses], scars, points for lesions of all regions involved)
- The distance between lesions, in particular the longest distance between two relevant lesions (i.e., nodules and fistulas in each region or size if only one lesion present)

Hidradenitis Suppurativa

- The presence of normal skin in between lesions (i.e., are all lesions clearly separated by normal skin?)

Points are accumulated in each of the above categories and added to give both a regional and total score. In addition, the authors recommend adding a visual analog scale for pain or using the dermatology life quality index (DLQI, or the Skindex) when assessing HS.

Previous review:

From the ICD-10 Dermatology review:

1) HYDRADENITIS SUPPURATIVA; DISSECTING CELLULITIS OF THE SCALP

Both of these conditions are very resistant to treatment. The severity may be reduced with oral isotretinoin, antibiotics, dapson, and injected or systemic steroids.

Category 7.

Impact on Healthy Life Years 2

Impact on Pain and Suffering 3

Population effects 0

Vulnerable populations 0

Tertiary prevention 1 (decreases risk of scarring down axilla; abscesses; but surgery end stage decision, cure, but 50% graft entire axilla and get disease around graft)

Effectiveness 1

Need for treatment 1

Net cost 4

SCORE 120, PUTS ON LINE 550

From Dr. Young:

Patients afflicted with this disease have purulent filled nodules abscesses with sinus tracts. It typically affects the groin, armpits, and under the breasts. It causes difficulty with walking, using the restroom, personal intimacy, and self-image/depression. This has caused many people to seek disability benefits (due to limiting ability to be employed and work) and has possibly contributed to narcotic use for pain control in some cases.

Until recently, all we had to offer were treatments that made minimal impact on patients. However, there is a new FDA approved biologic treatment which is making a significant impact on people's lives. We live in a very hopeful time where we can have treatments like this which make such a remarkable difference in people's lives. No doubt that this will allow us to have fewer people on disability benefits.

I humbly request that you consider covering this new treatment for HS in moderate to severe cases by covering it with an "above the line" designation.

From Ms. Christensen,

I am writing to request your consideration of hidradenitis suppurativa as a covered diagnosis for patients enrolled in your insurance plans.

This request is medically necessary for the following reasons:

Hidradenitis Suppurativa

- It is a painful condition
- It increases the risk of infection
- It causes emotional and physical distress

It will assist the individual to achieve or maintain maximum functional capacity in performing daily activities. Many of my patients who have this diagnosis have to take days off of work and make multiple trips to the emergency department due to pain and to have incision and drainage procedures. This increases the risk of infection and are expensive healthcare visits which could be properly managed at a medical clinic. Pain medications are becoming the standard treatment used to manage this condition due to the lack of coverage and additional treatment options that are not currently covered.

Please take into count the financial toll this condition can have on our communities and on the individuals suffering with this condition as you consider this diagnosis for coverage on your insurance plans.

From Dr. Moore:

I am writing to advocate for inclusion of Hidradenitis Suppurativa (ICD10 L73.2) as an above-the-line diagnosis for Oregon Medicaid patients. I am regrettably unable to attend the meeting, but I submit this message in the hopes it will be shared with the committee and considered in the discussion.

Hidradenitis Suppurativa is a chronic inflammatory disease that primarily affects the skin of intertriginous areas such as the axillae, inframammary skin, groin folds, inner thighs, and buttocks. It begins with small pustules and inflammatory nodules that may lead to sterile (non-infectious) abscesses in deeper portions of the skin. These abscesses are usually painful, and require treatment by a physician with drainage or injection of anti-inflammatory medication. When they occur on the buttocks or in groin fold areas, it makes sitting for long periods of time very painful for the patient. As this process recurs over time, these repeated nodules and abscesses can lead to formation of sinus tracts that chronically drain pus and malodorous fluid. Scars eventually form in the diseased areas, creating disfiguration of the skin and as painful or restricted movement of the limbs. In severe and long-standing disease, there is increased risk for skin cancer in the affected areas. Patients with this disease live with chronic malodorous discharge from their skin that is beyond their control, as well as painful recurring nodules in sensitive areas; this leads to social isolation, difficulty in pursuing romantic relationships, higher rates of depression, and overall poor quality of life. When their disease flares, they have loss of wages due to need for visits to their physician's office or an urgent care / emergency setting. These patients have a high level of need for medical care, which if uncovered or below-the-line, creates a significant economic burden to them. This condition is also often under-recognized or mis-diagnosed as recurrent infections, which may lead to inappropriate treatment. There is often a delay of several years before an accurate diagnosis is made.

Treatment of this condition involves incision and drainage of painful nodules, topical and oral antibiotics (tetracycline, a combination of clindamycin and rifampicin) or immunomodulating agents (acitretin, isotretinoin, dapsone, and cyclosporine). In severe disease with sinus tracts and scarring, surgery is often necessary, though the disease can recur at the sites of surgery. Early recognition and treatment of the disease may help to prevent further flares and

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slow or stall progression of the disease to more severe and costly states. Furthermore, accurate diagnosis and treatment by a specialist may improve patient's quality of life and reduce their medical economic burden.

If Hidradenitis Suppurativa is listed as an above-the-line condition, I expect patients with Oregon Medicaid will get diagnosed earlier, as they will be referred to the appropriate specialist in a more timely fashion. This will also facilitate more appropriate treatment, less costly visits to an emergent care facility, and improved quality of life for these patients. Hopefully earlier intervention will help to slow down or stall progression of the disease, and limit the need for costly hospitalizations and surgeries. I believe this will lead to less cost to the system overall.

From Dr. Dhossche:

HS is a chronic, debilitating disease, and those affected experience worsening quality of life measures the worse the disease. For mild to moderate disease, topical clindamycin and oral antibiotics have been shown to be helpful in small studies. Intralesional steroids have been shown to be helpful at least in the short term with individual flaring lesions. For moderate to severe disease, surgery has traditionally been pursued, but biologics offer a new avenue of treatment, with adalimumab being the most studied and having moderate quality evidence behind its use. Infliximab has in smaller studies been shown to improve quality of life.

Given the evidence presented regarding the personal and societal impact of hidradenitis suppurativa, as well as the range of treatments available, I am advocating for the coverage of hidradenitis suppurativa by Oregon Health Plan. Our patients with this disease suffer greatly. Please do the right thing for them.

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Evidence

1) OHA P&T 2018, review of adalimumab for HS

- a. Evidence for adalimumab in HS comes from two phase 3 trials and a systematic review from the Cochrane Collaboration. A technology appraisal of adalimumab in HS was also completed by the National Institute for Health and Care Excellence (NICE).
 - i. Two phase 3 trials (PIONEER 1 and PIONEER 2): Both trials were manufacturer-funded and the manufacturer participated in data collection, data analysis, data interpretation, and manuscript writing, review, and approval. Additionally, all of the authors disclosed potential conflicts of interest including conflicts specific to the manufacturer (such as employment, consulting fees, grant support, honoraria, etc.).
 - ii. Patients enrolled in both PIONEER 1 (n=307) and PIONEER 2 (n=326) had moderate to severe HS. Both trials ran for 36 weeks
- b. Effectiveness
 - i. There is low quality evidence from 2 randomized controlled trials (RCTs) that adalimumab 40 mg weekly improves the proportion of patients achieving a Hidradenitis Suppurativa Clinical Response (HiSCR), defined as at least a 50% reduction in total abscess and inflammatory nodule count from baseline with no increase in the abscess or draining-fistula count, compared to placebo at 12 weeks (41.8% vs. 26.0%, respectively, number needed to treat [NNT] 7; and 58.9% vs. 27.6%, NNT 4).
 - ii. There is insufficient evidence from 2 conflicting RCTs that adalimumab 40 mg weekly increases the proportion of patients with a 0-2 total abscess and inflammatory-nodule count at week 12 for patients with Hurley stage 2 disease at baseline compared to placebo (28.9% vs. 28.6%, respectively, p=0.96; and 51.8% vs. 32.2%, respectively, p=0.01, NNT 6).
 - iii. There is insufficient evidence from 2 conflicting RCTs that adalimumab 40 mg weekly increases the proportion of patients with at least 30% reduction and at least 1 unit reduction in pain score from baseline compared to placebo at week 12 (27.9% vs. 24.8%, respectively, p=0.63; and 45.7% vs. 20.7%, respectively, p<0.001, NNT 4). Clinical significance of a 30% reduction is unclear and it has been suggested that a 50% reduction in baseline pain is considered clinically meaningful.
 - iv. There is insufficient evidence from 2 conflicting RCTs that adalimumab 40 mg weekly improves the mean change in modified Sartorius score compared to placebo from baseline to week 12 (-24.4 points vs. -15.7 points, respectively, p=0.12; and -28.9 points vs. -9.5 points, respectively, p<0.001).
 - v. There is moderate quality evidence that adalimumab 40 mg weekly improves the Dermatology Life Quality Index (DLQI) score compared to placebo in moderate to severe HS at week 12 and week 16. Evidence from 2 RCTs found decreases of 5.4 points and 5.1 points with adalimumab compared with decreases of 2.9 points and 2.3 points with placebo at 12 weeks. The differences between placebo and adalimumab group changes do not meet the suggested minimum clinically significant difference of 4-5 points. Additionally, another RCT assessed in the Cochrane review found a benefit with adalimumab compared to placebo at 16 weeks in DLQI score (mean difference 4 points; 95% confidence interval [CI], 6.5 to 1.5 points lower).

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- vi. There is insufficient evidence to determine the effect of adalimumab on the need for surgery from clinical trials. However, NICE guidance based on post-hoc analyses of draining fistulas and non-draining fistulas concludes there is a decreased need for some types of surgical procedures (likely minor surgeries such as narrow margin excisions and incision and drainage procedures). No definite conclusions could be made on the effect of adalimumab on surgical-inpatient admissions. The post hoc analysis assessed by NICE found that a greater proportion of patients treated with adalimumab as compared to placebo had improvement in draining fistulas (33% vs. 19%; $p < 0.001$; NNT 8) and non-draining fistulas (15% vs. 9%; $p = 0.017$; NNT 17).
- c. Adverse events
 - i. There is low quality evidence that adalimumab 40 mg weekly and placebo have similar risks of serious adverse events [SAEs] (1.3%-1.8% vs. 1.3%-3.7%, respectively; RCT = 2), infections (24.8%-25.2% vs. 28.3%-32.5%, respectively; RCT = 2), and serious infections (0.6-0.7% vs. 0-1.2%, respectively; RCT = 2) through 12 weeks.
 - ii. There is low quality of evidence from patients who remained continuously on the respective treatment that adalimumab-treated patients have a similar risk of SAE at 12-36 weeks of therapy compared to placebo (2.1-3.9% vs. 4.6%, respectively; RCT=2 for adalimumab and 1 for placebo). Similarly, there is low quality of evidence in the same time frame that adalimumab- and placebo-treated patients have similar risk for serious infections (0-2.0% vs. 1.3%; RCT=2 for adalimumab and 1 for placebo). This evidence is limited by a high rate of overall attrition (41.3% and 52.8% for the two RCTs).
 - iii. There is insufficient evidence to determine the long-term safety of adalimumab for HS beyond 36 weeks. However, the safety profile of adalimumab dosed every other week for other conditions has been well characterized since the drug's initial U.S. approval in 2002. Like other immunosuppressants, adalimumab has FDA boxed warnings for serious infections and malignancies.
- d. Possible PA criteria for adalimumab if HS is moved to a funded line:
 - i. Require trial and failure, intolerance, or contraindication to conventional therapy (such as oral antibiotics) and
 - ii. Require evidence of response (a reduction of 25% or more in the total abscess and inflammatory nodule count and no increase in abscesses and draining fistulas) for renewal of authorization.

Cost:

Adalimumab wholesale acquisition cost: \$8,882/month at the weekly dosing recommended for use for HS (\$106,584 annual cost). It is unclear how long an optimal course of therapy is for HS.

Current utilization:

Despite being a below the line condition, HS had a significant number of paid claims for 2016.

-1324 individuals with claims for dates of service in CY2016, FFS and CCO. 6974 paid clean claims had this diagnosis (not necessarily as primary).

-Claims were for a variety of services, including office visits, ER visits, drainage of abscesses, excision of skin lesions, and skin grafts

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-total paid was approximately \$1.2 million for this diagnosis in 2016

Other coverage for adalimumab for HS:

- 1) **NICE 2016** <https://www.nice.org.uk/guidance/ta392/resources/adalimumab-for-treating-moderate-to-severe-hidradenitis-suppurativa-pdf-82602906813637>
 - a. Adalimumab is recommended, within its marketing authorisation, as an option for treating active moderate to severe hidradenitis suppurativa in adults whose disease has not responded to conventional systemic therapy. The drug is recommended only if the company provides it at the price agreed in the patient access scheme.
 - b. Assess the response to adalimumab after 12 weeks of treatment, and only continue if there is clear evidence of response, defined as:
 1. a reduction of 25% or more in the total abscess and inflammatory nodule count and
 2. no increase in abscesses and draining fistulas.
- 2) **Aetna 2017** policy on adalimumab (Humira): Hidradenitis suppurativa - Treatment of moderate to severe hidradenitis suppurativa (Hurley Stage II or Hurley Stage III) (see appendix) in persons who have had an inadequate response to at least a 90 day treatment of oral antibiotics for treatment of hidradenitis suppurativa, unless contraindicated

Hidradenitis Suppurativa

HERC staff summary:

Hidradenitis suppurativa (HS), in its severe forms, is a serious, disabling disease. Previously there were no treatments that were considered reasonably effective for HS; however, since the last review of HS, adalimumab received FDA approval for treating HS. There is moderate quality evidence (based on two manufacturer sponsored and influenced studies with a total N=632) that adalimumab improves the proportion of patients achieving at least 50% reduction in total abscess and inflammatory nodule count and improves the Dermatology Quality of Life Index (CQLI), although the increase in DQLI was below the level felt to be clinically meaningful. There is insufficient evidence to determine if adalimumab decreases pain or reduces need for surgery or surgical hospitalization.

OHP is already paying for a considerable volume of care for patients with HS, but this would be expected to increase if HS was moved above the funding line unless office treatment could significantly reduce the rate of ER visits, surgical procedures or other complications. An estimated 1500 OHP patients have HS based on claims data.

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HERC staff recommendation:

Consider re-prioritization of hidradenitis suppurativa based on the development of newer, more effective therapies

If re-prioritization is desired, HERC staff have identified two possible options:

- 1) **Option 1:** create an entirely new line as shown below, with the new guideline and scoring as shown below
 - a. Leave ICD-10 L73.2 (Hidradenitis suppurativa) on line 512 for cases not meeting the new guideline requirements, and rename this line 512 MILD HIDRADENITIS SUPPURATIVA; DISSECTING CELLULITIS OF THE SCALP

Line XXX MODERATE TO SEVERE HYDRADENITIS SUPPURATIVA

Treatment: MEDICAL AND SURGICAL THERAPY

ICD-10 codes: L73.2 (Hidradenitis suppurativa)

CPT/HCPCS codes: those currently appearing on line 512 HIDRADENITIS SUPPURATIVA; DISSECTING CELLULITIS OF THE SCALP

GUIDELINE NOTE XXX HIDRADENITIS SUPPURATIVA

Line XXX, 512

Hidradenitis suppurativa is included on line XXX only for moderate to severe disease (e.g. Hurley Stage II or Hurley Stage III); otherwise this condition is included on line 512.

Initial treatment with adalimumab is limited to adults whose disease has not responded to at least a 90-day trial of conventional therapy (e.g., oral antibiotics), unless such a trial is not tolerated or contraindicated. Treatment with adalimumab after 12 weeks is only included on line XXX for patients with a clear evidence of response, defined as:

1. a reduction of 25% or more in the total abscess and inflammatory nodule count, AND
2. no increase in abscesses and draining fistulas.

HERC staff proposed line scoring (current scores for line 512 in parentheses)

Category 7 (7)

Impact on Healthy Life Years 3 (2)

Impact on Pain and Suffering 4 (3)

Population effects 0 (0)

Vulnerable populations 0 (0)

Tertiary prevention 2 (1) (decreases risk of scarring down axilla; abscesses)

Effectiveness 2 (1)

Need for treatment 1 (1)

Net cost 2 (4)

SCORE 360 (120), approximate LINE 418 (512)

Current funding line is 469

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- 2) **Option 2:** add hidradenitis suppurativa to the new severe acne line created for the 2020 Biennial Review Prioritized List
- Rename this line to reflect the additional diagnoses, add ICD-10 and CPT codes as noted below
 - Leave ICD-10 L73.2 (Hidradenitis suppurativa) on line 512 for cases not meeting the new guideline requirements, and rename this line 512 MILD HIDRADENITIS SUPPURATIVA; DISSECTING CELLULITIS OF THE SCALP
 - Include the new guideline note for hidradenitis suppurativa as in option 1
 - The severe cystic acne line previously was scored to approximately line 451

Line XXX SEVERE CYSTIC ACNE; MODERATE TO SEVERE HYDRADENITIS SUPPURATIVA

Treatment: MEDICAL AND SURGICAL TREATMENT

- ICD-10 codes: L70 (acne), L73.2 (Hidradenitis suppurativa)
- CPT/HCPCS codes: all included currently on line 373 ACNE CONGLOBATA (SEVERE CYSTIC ACNE); those currently appearing on line 512 HIDRADENITIS SUPPURATIVA; DISSECTING CELLULITIS OF THE SCALP [this would include a series of CPT codes for “Excision of skin and subcutaneous tissue for hidradenitis”

GUIDELINE NOTE XXX HYDRADENITIS SUPPURATIVA

Line [severe cystic acne line], 512

Hidradenitis suppurativa is included on line [severe acne line] only for moderate to severe disease (e.g. Hurley Stage II or Hurley Stage III); otherwise this condition is included on line 512.

Initial treatment with adalimumab is limited to adults whose disease has not responded to at least a 90 day trial of conventional therapy (e.g. oral antibiotics), unless such a trial is not tolerated or contraindicated. Treatment with adalimumab after 12 weeks is only included on line XXX for patients with a clear evidence of response, defined as:

- a reduction of 25% or more in the total abscess and inflammatory nodule count, AND
- no increase in abscesses and draining fistulas.

From August, 2018:

Line scoring

Current scoring in parentheses for lines 373 ACNE CONGLOBATA (SEVERE CYSTIC ACNE)/530 ROSACEA; ACNE

Category 7 (7,7)

Impact on Healthy Life Years 1 (2,1)

Impact on Pain and Suffering 3 (3,2)

Population effects 0 (0)

Vulnerable populations 0 (0)

Tertiary prevention 0 (2,0)

Effectiveness 4 (4,4)

Need for treatment 0.8 (1,0.5)

Net cost 3 (3,3)

SCORE 256, PUTS ON LINE 451

Indication Review: Humira® (adalimumab) for Hidradenitis Suppurativa

Date of Review: November 2018

End Date of Literature Search: 8/2/2018

Purpose for Indication Review: To evaluate evidence for Humira® (adalimumab) in the setting of hidradenitis suppurativa (HS) as requested by the Health Evidence Review Commission (HERC). Medical therapy for HS is currently not funded by the Oregon Health Authority (OHA).¹

Research Questions:

1. What is the efficacy and effectiveness of adalimumab in treating HS?
2. What are the comparative harms of adalimumab in patients with HS?

Conclusions:

- Evidence for adalimumab in HS comes from two phase 3 trials² and a systematic review from the Cochrane Collaboration.³ A technology appraisal of adalimumab in HS was also completed by the National Institute for Health and Care Excellence (NICE).⁴ The evidence is applicable to Medicaid patients; however, no subgroup analyses specific to Medicaid patients were provided in any of the studies reviewed.
- There is low quality evidence from 2 randomized controlled trials (RCT) that adalimumab 40 mg weekly improves the proportion of patients achieving a Hidradenitis Suppurativa Clinical Response (HiSCR), defined as at least a 50% reduction in total abscess and inflammatory nodule count from baseline with no increase in the abscess or draining-fistula count, compared to placebo at 12 weeks (41.8% vs. 26.0%, respectively, number needed to treat [NNT] 7; and 58.9% vs. 27.6%, NNT 4).²
- There is insufficient evidence from 2 conflicting RCTs that adalimumab 40 mg weekly increases the proportion of patients with a 0-2 total abscess and inflammatory-nodule count at week 12 for patients with Hurley stage 2 disease at baseline compared to placebo (28.9% vs. 28.6%, respectively, $p=0.96$; and 51.8% vs. 32.2%, respectively, $p=0.01$, NNT 6).² The Hurley staging system ranges from stage 1 (least severe) to stage 3 (most severe), with stage 2 indicating recurrent abscesses with tract formation and cicatrization, single or multiple, and widely separated lesions.⁵
- There is insufficient evidence from 2 conflicting RCTs that adalimumab 40 mg weekly increases the proportion of patients with at least 30% reduction and at least 1 unit reduction in pain score from baseline compared to placebo at week 12 (27.9% vs. 24.8%, respectively, $p=0.63$; and 45.7% vs. 20.7%, respectively, $p<0.001$, NNT 4).² Clinical significance of a 30% reduction is unclear and it has been suggested that a 50% reduction in baseline pain is considered clinically meaningful.⁴
- There is insufficient evidence from 2 conflicting RCTs that adalimumab 40 mg weekly improves the mean change in modified Sartorius score compared to placebo from baseline to week 12 (-24.4 points vs. -15.7 points, respectively, $p=0.12$; and -28.9 points vs. -9.5 points, respectively, $p<0.001$).² Points for this scale are assigned in categories which include anatomical regions involved (3 points per region involved), number and scores of lesions (2 points for nodules,

4 for fistulas, 1 for scars, and 1 for others), the longest distance between two relevant lesions (<5 cm, 2 points; <10 cm, 4 points; ≥10 cm, 8 points), and if all lesions are clearly separated by normal skin (for each region: yes, 0 points; no, 6 points).^{6,7} There is no upper limit and a larger score indicates more severe disease, but the definition of a minimum clinically significant change is unclear.⁸

- Differences in efficacy outcome results between the two trials may be due to differences in baseline characteristics, antibiotic use, and geographic distribution of patients.² A greater benefit for several outcomes was seen in PIONEER 2, in which the patients had less severe disease and were able to continue on stable doses of tetracycline antibiotics.²
- There is moderate quality evidence that adalimumab 40 mg weekly improves the Dermatology Life Quality Index (DLQI) score compared to placebo in moderate to severe HS at week 12 and week 16. Evidence from 2 RCTs found decreases of 5.4 points and 5.1 points with adalimumab compared with decreases of 2.9 points and 2.3 points with placebo at 12 weeks.² The differences between placebo and adalimumab group changes do not meet the suggested minimum clinically significant difference of 4-5 points.^{2,4} Additionally, another RCT assessed in the Cochrane review found a benefit with adalimumab compared to placebo at 16 weeks in DLQI score (mean difference 4 points; 95% confidence interval [CI], 6.5 to 1.5 points lower).^{3,9} The DLQI questionnaire consists of 10 quality of life questions each ranked from 0 to 3, with a max score of 30 indicating the skin disease has a very large impact on the patient's quality of life.¹⁰ A change of 0-1 points indicates no effect; 2-5 points a small effect; 6-10 points a moderate effect; 11-20 points a large effect; and 21-30 an extremely large effect.¹¹
- There is insufficient evidence to determine the effect of adalimumab on the need for surgery from clinical trials. However, NICE guidance based on post-hoc analyses of draining fistulas and non-draining fistulas concludes there is a decreased need for some types of surgical procedures (likely minor surgeries such as narrow margin excisions and incision and drainage procedures).⁴ No definite conclusions could be made on the effect of adalimumab on surgical-inpatient admissions.⁴ The post hoc analysis assessed by NICE found that a greater proportion of patients treated with adalimumab as compared to placebo had improvement in draining fistulas (33% vs. 19%; p<0.001; NNT 8) and non-draining fistulas (15% vs. 9%; p=0.017; NNT 17).^{4,12}
- There is low quality evidence that adalimumab 40 mg weekly and placebo have similar risks of serious adverse events [SAEs] (1.3%-1.8% vs. 1.3%-3.7%, respectively; RCT = 2), infections (24.8%-25.2% vs. 28.3%-32.5%, respectively; RCT = 2), and serious infections (0.6-0.7% vs. 0-1.2%, respectively; RCT = 2) through 12 weeks.²
- There is low quality of evidence from patients who remained continuously on the respective treatment that adalimumab-treated patients have a similar risk of SAE at 12-36 weeks of therapy compared to placebo (2.1-3.9% vs. 4.6%, respectively; RCT=2 for adalimumab and 1 for placebo).² Similarly, there is low quality of evidence in the same time frame that adalimumab- and placebo-treated patients have similar risk for serious infections (0-2.0% vs. 1.3%; RCT=2 for adalimumab and 1 for placebo).² This evidence is limited by a high rate of overall attrition (41.3% and 52.8% for the two RCTs).²
- Long-term safety data for adalimumab in HS is limited to 36 weeks in RCTs and an additional 60 weeks in a subsequent open-label extension study.^{2,13} The safety profile of adalimumab dosed every other week for other conditions has been well characterized since the drug's initial U.S. approval in 2002.¹⁴ Like other immunosuppressants, adalimumab has FDA boxed warnings for serious infections and malignancies.¹⁴
- NICE guidance recommend adalimumab as an option for treating active moderate to severe HS in adults whose disease has not responded to conventional systemic therapy.⁴ It is recommended to assess response to treatment after 12 weeks of treatment, and only continue treatment if there is a reduction of 25% or more in total abscess and inflammatory nodule count and no increase in abscesses and draining fistulas.⁴
- In October 2018, the indication for adalimumab in moderate to severe hidradenitis suppurativa was expanded to include patients age 12 years and older.¹⁵

Recommendations:

- No further review or research needed at this time.

Background:

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease which has a prevalence of 1-4% worldwide and is 3 times more common in women than men.^{7,16} The mean age of onset is 22 years.¹⁶ It is characterized by inflamed nodules which occur most frequently in the axillary, inguinal, and anogenital regions of the body.^{7,16} These nodules are painful, recurrent, and can result in abscesses, chronic draining sinus tracts, scarring, disfigurement, and disability.¹⁶ Genetic predisposition, hormonal factors, immune factors, medications such as lithium and medroxyprogesterone acetate, obesity, and smoking all are potential contributors to the etiology.¹⁶

There are multiple staging systems that evaluate symptoms and severity of HS. The Hurley clinical staging system describes disease severity by 3 stages: stage 1 indicates abscess formation, single or multiple, without sinus tracts and cicatrization (scar formation); stage 2 indicates recurrent abscesses with tract formation and cicatrization, single or multiple, widely separated lesions; and stage 3 indicates diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across the entire area.⁵ About 69% of patients have stage 1 disease, while approximately 28% and 4% of patients have more severe stage 2 and 3 disease.⁵ The minimum clinically significant change in Hurley staging is unclear.¹⁷

The modified Sartorius score is another method of determining severity in which individual nodules and fistulas are counted.⁵ Points are assigned in categories which include anatomical regions involved (3 points per region involved), number and scores of lesions (2 points for nodules, 4 for fistulas, 1 for scars, and 1 for others), the longest distance between two relevant lesions (<5 cm, 2 points; <10 cm, 4 points; ≥ 10 cm, 8 points), and if all lesions are clearly separated by normal skin (for each region: yes, 0 points; no, 6 points).^{6,7} There is no upper limit as scoring depends on the individual patient's lesions, and a larger score indicates more severe disease.⁸ The definition of a minimum clinically important change in this score is unclear.¹⁷

The Hidradenitis Suppurativa Physician's Global Assessment (HS-PGA) is another scale utilized which stages severity as clear (no inflammatory or non-inflammatory nodules), minimal (only non-inflammatory nodules), mild (<5 inflammatory nodules or 1 abscess or draining fistula and no inflammatory nodules), moderate (<5 inflammatory nodules or one abscess or draining fistula and ≥ 1 inflammatory nodules or 2-5 abscesses or draining fistulas and <10 inflammatory nodules), severe (2-5 abscesses or draining fistulas and ≥ 10 inflammatory nodules), or very severe (more than 5 abscesses or draining fistulas).^{5,18}

The Hidradenitis Suppurativa Clinical Response (HiSCR) measure incorporates the status of lesions: abscesses (fluctuant, with or without drainage, tender or painful), inflammatory nodules (tender, erythematous, pyogenic granuloma lesion), and draining fistulas (sinus tracts, with communications to skin surface, draining purulent fluid).¹⁹ A responder is identified as having a 50% or greater reduction in abscesses and inflammatory nodules, no increase in the number of abscesses, and no increase in the number of draining fistulas from baseline.¹⁹ However, the minimum clinically important difference is unclear.⁴ A 25% reduction in total abscess and inflammatory nodules may also reflect a partial response to treatment.⁴

The Dermatology Life Quality Index (DLQI) can be used to determine quality of life. The questionnaire consists of 10 quality of life questions, each ranked from 0 to 3, with a maximum score of 30 indicating the skin disease has a very large negative impact on the patient's quality of life.¹⁰ A change of 0-1 points indicates no effect; 2-5 points a small effect; 6-10 points a moderate effect; 11-20 points a large effect; and 21-30 points an extremely large effect.¹¹ It has been suggested that a change of 4 or 5 points may be the minimum clinically important difference, but this scale may underestimate effects of treatment in patients who have developed coping mechanisms for the disease.^{2,4} Patient-reported pain scales are also used to determine disease severity and effects of treatment, and a reduction of 50% from baseline in pain scores may be considered clinically meaningful.⁴

Nonpharmacological treatments for HS include local hygiene and cleansing, reducing heat, humidity, and friction in the area, weight loss to ideal weight, and smoking cessation.¹⁶ Surgical treatment may also be an option for Hurley stage 2 and 3 patients.¹⁶ Pharmacological treatments for HS include antibiotics, retinoids, corticosteroids, and immunosuppressive agents such as tumor necrosis factor (TNF)-alpha inhibitors.^{5,16} However, the most commonly used treatments are topical and oral antibiotics.⁴ Antibiotics can be used both for the acute treatment of an infected area as well as for maintenance treatment.^{7,16,20} The most commonly used oral antibiotic treatments are tetracyclines.⁴ The next most commonly utilized therapies are acitretin, isotretinoin, dapsone, and cyclosporine.⁴

TNF-alpha inhibitors are often reserved for patients with moderate to severe HS.^{5,16} Guidance from NICE recommends the use of adalimumab for active moderate to severe HS in adults whose disease has not responded to conventional systemic therapy.⁴ Continuation of therapy beyond 12 weeks is recommended only if there is a reduction of 25% or more in the total abscess and inflammatory nodule count as well as no increase in abscesses or draining fistulas at that time.⁴

Adalimumab was approved for moderate to severe HS in September 2015 and is the only medication FDA-approved for this condition.¹⁴ Adalimumab is administered with a loading dose of 160 mg subcutaneously followed by a second dose of 80 mg two weeks later (Day 15) and then 40 mg for the third (Day 29) and subsequent weekly doses.¹⁴ In October 2018, the indication was expanded to include patients age 12 years and older, with varied dosing based on weight.¹⁵ Medical therapy for HS currently appears in the unfunded region of the Oregon Health Authority's Prioritized List of Health Services.¹

Randomized Controlled Trials:

A total of 26 citations were manually reviewed from the initial literature search for the HS indication review. After further review, 25 citations were excluded because of wrong study design (e.g., observational or phase 2 trial when phase 3 trials available), comparator (e.g., no control or placebo-controlled), outcome studied (e.g., non-clinical), or already being included in a systematic review within the indication review. The one included citation was the PIONEER 1 and PIONEER 2 study manuscript, described below.

Clinical Efficacy:

Clinical Trials

Adalimumab, a TNF-alpha inhibitor, is approved by the FDA for the treatment of moderate to severe HS.¹⁴ Two phase 3 trials (PIONEER 1 and PIONEER 2) provide efficacy and safety data for adalimumab in HS compared to placebo.² Both trials were manufacturer-funded and the manufacturer participated in data collection, data analysis, data interpretation, and manuscript writing, review, and approval.² Additionally, all of the authors disclosed potential conflicts of interest including conflicts specific to the manufacturer (such as employment, consulting fees, grant support, honoraria, etc.).²

The methods and trial design for PIONEER 1 and PIONEER 2 were similar.² Both trials were composed of 2 periods which compared adalimumab to placebo. In the first period, adalimumab was dosed at 160 mg at week 0, 80 mg at week 2, and 40 mg weekly at 4 through 12 weeks.² In the second period, patients who had been randomized to adalimumab in the first period underwent re-randomization to either adalimumab weekly, adalimumab 40 mg every other week, or placebo.² Patients randomized to placebo in the first period were reassigned in a blinded fashion in period 2 to either adalimumab 160 mg at week 12, 80 mg at week 14, followed by 40 mg weekly starting at week 16 (in PIONEER 1) or placebo beginning at week 12 (in PIONEER 2).² The second period lasted for a duration of 24 weeks, resulting in a total study duration of 36 weeks for period 1 and period 2 combined.² However, the primary and secondary efficacy endpoints were

all determined at week 12 which marked the end of period 1.² Patients enrolled in both PIONEER 1 (n=307) and PIONEER 2 (n=326) had moderate to severe HS and a duration of disease of at least one year.²

The primary efficacy endpoint was the proportion of patients with a HiSCR response, defined as at least a 50% reduction from baseline in total abscess and inflammatory nodule count, with no increase in the abscess or draining-fistula count.² Three ranked secondary endpoints included the proportion of patients with a total abscess and inflammatory-nodule count of 0, 1, or 2 for patients with Hurley stage 2 disease at baseline, at least 30% reduction and at least 1-unit reduction from baseline in pain score, and the change from baseline in modified Sartorius score.²

In PIONEER 1, HiSCR response at week 12 was achieved by a statistically significant greater proportion of adalimumab-treated patients compared to placebo-treated patients (41.8% vs. 26%, respectively; ARR 15.8%; NNT 7; p=0.003).² However, no statistically significant results were seen in the three ranked secondary endpoints.² No statistically significant difference was found between the number of adalimumab-treated and placebo-treated patients in the proportion of patients with a total abscess and inflammatory nodule count of 0, 1, or 2 at week 12 (28.9% vs. 28.6%, respectively; ARR 0.3%; 95% CI -13.4 to 14.1; p=0.96).² Similarly, no statistically significant difference was found in the proportion of patients with at least 30% reduction and at least 1-unit reduction from baseline in pain score between adalimumab and placebo groups at week 12 (27.9% vs. 24.8%, respectively; ARR 3.1%; 95% CI -8.6 to 14.2; p=0.63).² Finally, no statistically significant difference was found for the change in mean score from baseline in modified Sartorius score for either adalimumab or placebo group at week 12 (-24.4 points vs. -15.7 points, respectively; mean difference: -8.7 points; 95% CI -19.7 to 2.4; p=0.12).²

In PIONEER 2, HiSCR response at week 12 was achieved by a statistically significant greater proportion of adalimumab-treated patients compared to placebo-treated patients (58.9% vs 27.6%, respectively; ARR 31.3%; NNT 4; p<0.001).² In contrast to PIONEER 1, a statistically significant benefit was seen with adalimumab compared to placebo in the three ranked secondary outcomes.² A statistically significant difference was also found in the proportion of adalimumab- and placebo-treated patients with a total abscess and inflammatory nodule count of 0, 1, or 2 at week 12 (51.8% vs. 32.2%, respectively; ARR 19.6%; 95% CI 4.7 to 34.2; p=0.01; NNT 6).² Similarly, a statistically significant difference was found in the proportion of patients with at least 30% reduction and at least 1 unit reduction from baseline in pain score between adalimumab and placebo groups at week 12 (45.7% vs. 20.7%, respectively; ARR 25.1%; 95% CI 12.7 to 37.6; p<0.001; NNT 4).² A statistically significant difference was also found for the change in mean score from baseline in modified Sartorius score for either adalimumab or placebo group at week 12 (-28.9 points vs. -9.5 points, respectively; mean difference: -19.4 points; 95% CI -28.6 to -10.1; p<0.001).²

Differences in the results of the three ranked secondary endpoints, all non-statistically significant in PIONEER 1 yet all statistically significant in PIONEER 2, may be due to differences in baseline characteristics, antibiotic use, and geographic distribution of patients.² Patients in PIONEER 1 had higher mean abscess count (2.75 vs. 2.2, respectively), inflammatory nodule count (11.55 vs. 9, respectively) and draining fistula count (4.2 vs. 3.35, respectively) as well as higher mean modified Sartorius scores (149.1 vs. 115.1 points, respectively) compared to patients in PIONEER 2.² While patients were required to stop oral antibiotic treatment in PIONEER 1, patients who were on stable doses of tetracycline antibiotics were allowed to continue them in PIONEER 2.² Concomitant oral antibiotics were used by 19% of patients in PIONEER 2.² Approximately 50% of patients in PIONEER 1 were from the U.S., while only 27% of patients in PIONEER 2 were from the U.S., which limits applicability to the Oregon Medicaid population.² Other countries of origin for patients in PIONEER 1 included Australia, Canada, Czech Republic, Germany, and Hungary.² Other countries of origin for patients in PIONEER 2 included Australia, Canada, Denmark, France, Greece, the Netherlands, Puerto Rico, Sweden, Switzerland, and Turkey.²

Quality of life, as assessed by DLQI, was a non-ranked secondary endpoint for both PIONEER 1 and PIONEER 2.² Patients treated with adalimumab experienced greater improvements in DLQI score compared to placebo in both PIONEER 1 (-5.4 vs. -2.9, respectively) and PIONEER 2 (-5.1 and -2.3, respectively).² The minimum clinically significant difference is suggested to be around 4-5 points.^{2,4} Among patients with a baseline score of greater than or equal to 5 (>90% of patients in period 1), a decrease of 5 points was seen with a greater proportion of patients in the adalimumab groups compared to the placebo groups in both PIONEER 1 (50.7% vs. 33.8%, p=0.004, respectively) and PIONEER 2 (49% vs. 34%, p=0.011, respectively).²

Both PIONEER 1 and PIONEER 2 were rated as poor quality due to manufacturer involvement and attrition. There was low attrition in period 1 which encompassed the primary and ranked secondary endpoints (5.5% and 6.1%, respectively) but high attrition occurred with longer follow-up in period 2 (41.3% and 52.8%, respectively).² A majority of the attrition in period 2 for both trials was due to loss of response, worsening of symptoms, or absence of improvement.²

Systematic Reviews

A 2017 Cochrane review on treatments for HS evaluated RCTs through August 2015 for all interventions.³ Five of the eleven authors disclosed conflicts of interest related to the manufacturer of adalimumab (including advisory fees, honorarium, or acting as an investigator for a manufacturer-funded study).³ As the PIONEER 1 and PIONEER 2 trials discussed above were published in 2016, these were not included in this review.^{2,3} The review found moderate quality evidence that adalimumab 40 mg weekly improved the DLQI score compared to placebo in moderate to severe HS (difference: 4 points; 95% CI 6.5 to 1.5 points lower; studies = 1).³ However, the lower end of the 95% CI (1.5 points) may not be clinically significant and the overall effect (4 points) was small.³ This study of weekly adalimumab dosing was limited by not being powered to detect rare or delayed AEs.³ For adalimumab every other week dosing, a meta-analysis of two trials (n=124) found no difference between adalimumab and placebo in quality of life or secondary outcomes such as pain score, HS scoring systems, PGA, or duration of remission.³ The review concluded that results from the PIONEER studies may improve confidence in the effect size and safety of weekly adalimumab therapy.³

Guidelines

National Institute for Health and Care Excellence

In June 2016, NICE published a technology appraisal guidance for adalimumab in treating moderate to severe HS.⁴ This guidance evaluated both the clinical and cost effectiveness and provided recommendations for place in therapy.⁴ Clinical effectiveness was determined from the PIONEER 1 and 2 trials (described above).⁴ It was concluded that adalimumab provides a significant benefit for symptom improvement and quality of life compared to placebo in the short term, but have not been shown long term.⁴ The recommendations for use of adalimumab in HS were as follows:

- Adalimumab is recommended as an option for treating active moderate to severe HS in adults whose disease has not responded to conventional systemic therapy.⁴
- After 12 weeks of treatment, assess the response to adalimumab and only continue if there is clear evidence of response as defined as
 - a reduction of 25% or more in total abscess and inflammatory nodule count and
 - no increase in abscesses and draining fistulas.⁴

The definition of response in the recommendations based on a 25% or more reduction in total abscess and inflammatory nodule count differs from the 50% reduction in the PIONEER 1 and 2 primary endpoints.^{2,4} However, the clinical experts determined that the 50% reduction threshold was too high, and instead

determined that a 25% reduction in total abscess and inflammatory nodule count with no increase in abscesses or draining fistulas would reflect a treatment response.⁴

While the recommendations do not specify which conventional systemic therapies must be tried, the most commonly used treatments are topical and oral antibiotics.⁴ The most commonly used oral antibiotic is tetracycline, followed by a combination of clindamycin and rifampicin.⁴ The next most commonly utilized conventional therapies are acitretin, isotretinoin, dapsone, and cyclosporine.⁴

In the cost effectiveness analysis, the cost of surgical-inpatient admissions was a key consideration.⁴ However, there was a lack of data regarding surgeries in the PIONEER trials as surgery was not permitted in the trials per protocol.^{4,12} In response to a request from the evidence review group for outcome data on surgical procedures, the manufacturer completed a post-hoc analysis of pooled PIONEER 1 and 2 data.^{4,12} The post hoc analysis found that a greater proportion of patients treated with adalimumab as compared to placebo had improvement in draining fistulas (33% vs. 19%; $p < 0.001$; NNT 8) and non-draining fistulas (15% vs. 9%; $p = 0.017$; NNT 17).^{4,12} These outcomes would likely be associated with minor surgeries, such as narrow margin excisions and incision and drainage procedures, and therefore, the committee concluded that adalimumab reduces the need for some types of surgical procedures.⁴ However, based on the lack of robust evidence, no conclusions could be made on adalimumab's effect on surgical-inpatient admissions.⁴

Clinical Safety:

In PIONEER 1 and PIONEER 2 through week 12 (period 1), the proportions of patients with any adverse event (AE) were similar for adalimumab- and placebo-treated patients (50.3% vs. 58.6%, respectively in PIONEER 1; 57.1% vs. 63.2%, respectively in PIONEER 2).² The two AEs which occurred by week 12 in at least 10% of patients in either the adalimumab or placebo groups of either trial included headache (9.2% vs. 9.9%, respectively in PIONEER 1; 12.9% vs. 12.9%, respectively in PIONEER 2) and nasopharyngitis (5.9% vs. 10.5%, respectively in PIONEER 1; 5.5% vs. 6.1%, respectively in PIONEER 2).² SAEs reported by week 12 were similar or lower with adalimumab compared to placebo (1.3% vs. 1.3%, respectively for PIONEER 1; 1.8% vs. 3.7%, respectively for PIONEER 2).² Infections occurred at a lower rate by week 12 for adalimumab-treated patients compared to placebo-treated patients in both trials (24.8% vs. 28.3%, respectively for PIONEER 1; 25.2% vs. 32.5%, respectively for PIONEER 2) and rates of serious infections were also low and similar between groups (0.7% vs. 0%, respectively; 0.6% vs. 1.2%, respectively).²

Safety outcomes from period 2 (weeks 12-36) of PIONEER 1 and 2 are presented in **Table 1**.² For period 2 of both trials, high attrition was seen (41.3% and 52.8% for PIONEER 1 and PIONEER 2, respectively).²

Table 1: Selected Safety Outcomes in Period 2 (weeks 12-36) of PIONEER 1 and PIONEER 2.²

| Safety Outcome | PIONEER 1 | | | | PIONEER 2 | | | |
|----------------|--|----------------|------------------------------------|--------------------------|--|----------------|------------------------------------|--------------------------|
| | Adalimumab Weekly (n=145; reassigned from placebo in Period 1) | Placebo (n=49) | Adalimumab Every Other Week (n=48) | Adalimumab Weekly (n=48) | Placebo (n=151; reassigned from placebo in Period 1) | Placebo (n=51) | Adalimumab Every Other Week (n=53) | Adalimumab Weekly (n=51) |
| | | | | | | | | |

| | | | | | | | | |
|---|------------|------------|------------|------------|------------|------------|------------|------------|
| Any adverse event | 90 (62.1%) | 28 (57.1%) | 22 (45.8%) | 28 (58.3%) | 68 (45.0%) | 33 (64.7%) | 30 (56.6%) | 29 (56.9%) |
| Serious adverse events | 3 (2.1%) | 0 (0%) | 1 (2.1%) | 1 (2.1%) | 7 (4.6%) | 0 (0%) | 2 (3.8%) | 2 (3.9%) |
| Adverse events leading to study drug discontinuation | 5 (3.4%) | 1 (2.0%) | 0 (0%) | 0 (0%) | 3 (2.0%) | 0 (0%) | 1 (1.9%) | 1 (2.0%) |
| Infections | 43 (29.7%) | 16 (32.7%) | 12 (25.0%) | 14 (29.2%) | 35 (23.2%) | 13 (25.5%) | 19 (35.8%) | 18 (35.3%) |
| Serious infections | 1 (0.7%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (1.3%) | 0 (0%) | 0 (0%) | 1 (2.0%) |

An open-label extension trial following PIONEER 1 and 2 also studied safety for at least 60 weeks after the 36 week RCT period.¹³ In the population of patients which received adalimumab weekly throughout both the RCT and open-label extension trial periods (n=88), adverse events leading to treatment discontinuation occurred in 14.8% of patients (n=13) and serious adverse events occurred in 13.6% (n=12).¹³ Infections occurred in 71.6% of the patients (n=63) and serious infections occurred in 3.4% (n=3).¹³

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

- 1) Improvement in symptoms
- 2) Improvement in quality of life (DLQI)
- 3) Reduction in complications and surgeries
- 4) Serious adverse events
- 5) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Clinical response per HiSCR measure at week 12 (>50% reduction from baseline in total abscess and inflammatory-nodule count, with no increase in abscess or draining-fistula count)

Table 2. Comparative Evidence Table.

| Ref./ Study Design | Drug Regimens/ Duration | Patient Population | N | Efficacy Endpoints | ARR/NNT | Safety Outcomes | ARR/NNH | Risk of Bias/ Applicability |
|---|---|---|---|---|---------|---|------------|--|
| 1. Kimball et al. ² (PIONEER I) MC Phase 3, RCT with 2 DB, PC periods | <u>Period 1</u> 1. Adalimumab 160 mg at week 0, 80 mg at week 2, followed by 40 mg weekly starting at week 4 2. Placebo | <u>Demographics:</u> • Mean age: 37 y • Female: 64% • White: 76% • Median duration of HS: 9.1 y • Previous systemic therapy: 43% | <u>ITT:</u> <u>Period 1</u> Total: 307 1. 153 2. 154 <u>Period 2</u> Total: 290 1. 48 2. 48 | <u>Primary Endpoint:</u> Clinical response per HiSCR measure at week 12 (≥50% reduction from baseline in total abscess and inflammatory-nodule count, with no increase in abscess or draining-fistula count) 1. 41.8% | 15.8%/7 | <u>Period 1</u> <u>Serious AEs</u> 1. 2 (1.3%) 2. 2 (1.3%) <u>AEs Leading to DC</u> 1. 0 (0%) 2. 2 (1.3%) <u>Infection</u> | NA for all | Risk of Bias (low/high/unclear): <u>Selection Bias:</u> Low. Randomized centrally and treatments assigned by IVRS. Balanced characteristics at baseline. <u>Performance Bias:</u> Low. Matching placebo was used. Protocol was approved at each site. <u>Detection Bias:</u> Low. Investigator and study site personnel blinded. <u>Attrition Bias:</u> High. Overall high attrition for Period 2 (41.3%). Low attrition for Period 1 |

| | | | | | | | |
|--|---|--|---|---|-------------------------------|---|---|
| <p>36 weeks (period 1: 12 weeks; period 2: 24 weeks)</p> | <p>Period 2 <i>Pts previously assigned to adalimumab</i></p> <p>1. Adalimumab 40 mg weekly</p> <p>2. Adalimumab 40 mg every other week</p> <p>3. Placebo</p> <p><i>Pts previously assigned to placebo</i></p> <p>4. Adalimumab 160 mg at week 12, 80 mg at week 14, followed by 40 mg weekly starting at week 16</p> | <ul style="list-style-type: none"> • Prior surgery for HS: 11% • Total number of abscesses & inflammatory nodules: 14 • Modified Sartorius score: 149.1 <p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Age ≥ 18 y • HS ≥ 1 y • Moderate to severe HS (total abscess & inflammatory nodule count ≥ 3) at baseline • Inadequate response to oral antibiotics • Anti-TNF-a naïve <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Prior anti-TNF therapy • Any active skin disease or condition that could interfere with assessment of HS • Antibiotic treatment within 28 days of baseline • Receipt of prescription topical therapies for HS ≤ 14 days prior to baseline | <p>3. 49 4. 145</p> <p>Attrition: <i>Period 1:</i> Total: 17 (5.5%) 1. 8 (5.2%) 2. 9 (5.8%)</p> <p><i>Period 2:</i> Total: 120 (41.3%) 1. 20 (41.6%) 2. 21 (43.8%) 3. 27 (55.1%) 4. 52 (35.9%)</p> | <p>2. 26.0% P=0.003 RR & CI NR</p> <p>Secondary Endpoint: Total abscess and inflammatory-nodule count of 0, 1, or 2 in patients with Hurley stage II disease at week 12</p> <p>1. 24/83 (28.9%) 2. 24/84 (28.6%) Difference: 0.3 (95% CI - 13.4 to 14.1) P=0.96</p> <p>$\geq 30\%$ reduction and ≥ 1 unit reduction from baseline in pain score at week 12</p> <p>1. 34/122 (27.9%) 2. 27/109 (24.8%) Difference: 2.8 (95% CI -8.6 to 14.2) P=0.63</p> <p>Change in mean score from baseline in modified Sartorius score at week 12</p> <p>1. -24.4 2. -15.7 Difference: -8.7 (95% CI - 19.7 to 2.4) P=0.12</p> | <p>NA</p> <p>NA</p> <p>NA</p> | <p>1. 38 (24.8%) 2. 43 (28.3%)</p> <p>Serious Infection 1. 1 (0.7%) 2. 0 (0%)</p> <p>Cancer 1. 0 (0%) 2. 1 (0.7%)</p> <p><i>Period 2</i> Serious AEs 1. 1 (2.1%) 2. 1 (2.1%) 3. 0 (0%) 4. 3 (2.1%)</p> <p>AEs Leading to DC 1. 0 (0%) 2. 0 (0%) 3. 1 (2.0%) 4. 5 (3.4%)</p> <p>Infection 1. 14 (29.2%) 2. 12 (25.0%) 3. 16 (32.7%) 4. 43 (29.7%)</p> <p>Serious Infection 1. 0 (0%) 2. 0 (0%) 3. 0 (0%) 4. 1 (0.7%)</p> <p>p-values, RR, 95% CI were NR</p> | <p>(5.5%) which was utilized for primary and ranked secondary outcomes. ITT used for efficacy analysis. LOCF utilized for analysis of missing continuous variables. Non-responder imputation utilized for analysis of missing categorical values.</p> <p>Reporting Bias: Unclear. Protocol available. Pre-specified primary and ranked secondary outcomes reported. Confidence intervals not reported for primary endpoint.</p> <p>Other Bias: High. Funded by AbbVie who participated in data collection, data analysis, data interpretation, and manuscript writing, review, and approval.</p> <p>Applicability: Patient: Moderate to severe HS at baseline appropriate for utilizing second-line therapies such as TNF-a inhibitors. Intervention: Adalimumab dosing appropriate and approved by FDA. Comparator: Placebo appropriate to establish efficacy. No other TNF-a inhibitor agents approved for this condition. Outcomes: Clinically meaningful symptom endpoints used appropriate for HS. However, minimum clinically important difference for this outcome is unclear. Majority of attrition in period 2 due to loss of response, worsening of symptoms, or absence of improvement. Setting: 50.5% of patients from the U.S. Other countries of origin included Australia, Canada, Czech Republic, Germany, and Hungary.</p> |
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|---|--|---|---|---|--|---|-------------------|---|
| | | <ul style="list-style-type: none"> • Receipt of systemic non-biologic therapies with potential impact on HS <28 days prior to baseline • Receipt of oral concomitant analgesics for HS pain ≤14 days prior to baseline | | | | | | |
| <p>2. Kimball et al.² (PIONEER II)</p> <p>MC Phase 3, RCT with 2 DB, PC periods</p> <p>36 weeks (period 1: 12 weeks; period 2: 24 weeks)</p> | <p><u>Period 1</u></p> <p>1. Adalimumab 160 mg at week 0, 80 mg at week 2, followed by 40 mg weekly starting at week 4</p> <p>2. Placebo</p> <p><u>Period 2</u></p> <p><i>Pts previously assigned to adalimumab</i></p> <p>1. Adalimumab 40 mg weekly</p> <p>2. Adalimumab 40 mg every other week</p> <p>3. Placebo</p> <p><i>Pts previously assigned to placebo</i></p> <p>4. Placebo</p> | <p><u>Demographics:</u></p> <ul style="list-style-type: none"> • Mean age: 35 y • Female: 68% • White: 84% • Median duration of HS: 9.5 y • Previous systemic therapy: 48% • Prior surgery for HS: 14% • Total number of abscesses & inflammatory nodules: 11 • Modified Sartorius score: 115.1 <p><u>Key Inclusion Criteria:</u></p> <ul style="list-style-type: none"> • See PIONEER 1 <p><u>Key Exclusion Criteria:</u></p> <ul style="list-style-type: none"> • Prior anti-TNF therapy • Any active skin disease or condition that could interfere | <p><u>ITT:</u></p> <p><i>Period 1</i></p> <p>Total: 326</p> <p>1. 163</p> <p>2. 163</p> <p><i>Period 2</i></p> <p>Total: 306</p> <p>1. 51</p> <p>2. 53</p> <p>3. 51</p> <p>4. 151</p> <p><u>Attrition:</u></p> <p><i>Period 1:</i></p> <p>Total: 20 (6.1%)</p> <p>1. 8 (4.9%)</p> <p>2. 12 (7.4%)</p> <p><i>Period 2:</i></p> <p>Total: 190 (52.8%)</p> <p>1. 23 (45.1%)</p> <p>2. 28 (52.8%)</p> | <p><u>Primary Endpoint:</u></p> <p>Clinical response per HiSCR measure at week 12 (≥50% reduction from baseline in total abscess and inflammatory-nodule count, with no increase in abscess or draining-fistula count)</p> <p>1. 58.9%</p> <p>2. 27.6%</p> <p>P<0.001</p> <p>RR & CI NR</p> <p><u>Secondary Endpoint:</u></p> <p>Total abscess and inflammatory-nodule count of 0, 1, or 2 in patients with Hurley stage II disease at week 12</p> <p>1. 44/85 (51.8%)</p> <p>2. 28/87 (32.2%)</p> <p>Difference: 19.5 (95% CI 4.7 to 34.2)</p> <p>P=0.01</p> <p>≥30% reduction and ≥1 unit reduction from baseline in pain score at week 12</p> <p>1. 48/105 (45.7%)</p> <p>2. 23/111 (20.7%)</p> | <p>31.3%/4</p> <p>19.6%/6</p> <p>25%/4</p> | <p><u>Outcome:</u></p> <p><i>Period 1</i></p> <p><u>Serious AEs</u></p> <p>1. 3 (1.8%)</p> <p>2. 6 (3.7%)</p> <p><u>AEs Leading to DC</u></p> <p>1. 4 (2.5%)</p> <p>2. 6 (3.7%)</p> <p><u>Infection</u></p> <p>1. 41 (25.2%)</p> <p>2. 53 (32.5%)</p> <p><u>Serious Infection</u></p> <p>1. 1 (0.6%)</p> <p>2. 2 (1.2%)</p> <p><u>Cancer</u></p> <p>1. 0 (0%)</p> <p>2. 0 (0%)</p> <p><i>Period 2</i></p> <p><u>Serious AEs</u></p> <p>1. 2 (3.9%)</p> <p>2. 2 (3.8%)</p> <p>3. 0 (0%)</p> <p>4. 7 (2.0%)</p> <p><u>AEs Leading to DC</u></p> | <p>NA for all</p> | <p>Risk of Bias (low/high/unclear):</p> <p><u>Selection Bias:</u> Low. See PIONEER 1.</p> <p><u>Performance Bias:</u> Low. See PIONEER 1.</p> <p><u>Detection Bias:</u> Low. See PIONEER 1.</p> <p><u>Attrition Bias:</u> High. Overall high attrition for Period 2 (52.8%). Low attrition for Period 1 (6.1%) which was utilized for primary and ranked secondary outcomes. ITT used for efficacy analysis. LOCF utilized for analysis of missing continuous variables. Non-responder imputation utilized for analysis of missing categorical values.</p> <p><u>Reporting Bias:</u> Unclear. See PIONEER 1.</p> <p><u>Other Bias:</u> High. See PIONEER 1.</p> <p>Applicability:</p> <p><u>Patient:</u> See PIONEER 1.</p> <p><u>Intervention:</u> See PIONEER 1.</p> <p><u>Comparator:</u> See PIONEER 1.</p> <p><u>Outcomes:</u> See PIONEER 1.</p> <p><u>Setting:</u> 27.3% of patients from the U.S. Other countries of origin included Australia, Canada, Denmark, France, Greece, the Netherlands, Puerto Rico, Sweden, Switzerland, and Turkey.</p> |

| | | | | | | | |
|--|--|---|---|--|-----------|--|--|
| | | <p>with assessment of HS</p> <ul style="list-style-type: none"> • Receipt of prescription topical therapies for HS \leq14 days prior to baseline • Receipt of systemic non-biologic therapies with potential impact on HS <28 days prior to baseline • Receipt of oral concomitant analgesics for HS pain \leq14 days prior to baseline | <p>3. 28 (54.9%) 4. 111 (73.5%)</p> | <p>Difference: 25.1 (95% CI 12.7 to 37.6) P<0.001</p> <p>Change in mean score from baseline in modified Sartorius score at week 12</p> <p>1. -28.9 2. -9.5 Difference: -19.4 (95% CI -28.6 to -10.1) P<0.001</p> | <p>NA</p> | <p>1. 1 (2.0%) 2. 1 (1.9%) 3. 0 (0%) 4. 3 (2.0%)</p> <p><u>Infection</u></p> <p>1. 18 (35.3%) 2. 19 (35.8%) 3. 13 (25.5%) 4. 35 (23.2%)</p> <p><u>Serious Infection</u></p> <p>1. 1 (2.0%) 2. 0 (0%) 3. 0 (0%) 4. 2 (1.3%)</p> <p>p-values, RR, 95% CI were NR</p> | |
|--|--|---|---|--|-----------|--|--|

Abbreviations [alphabetical order]: AE = adverse events; ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; DC = discontinuation; FDA = Food and Drug Administration; HiSCR = Hidradenitis Suppurativa Clinical Response; HS = hidradenitis suppurativa; ITT = intention to treat; IVRS = interactive voice-response system; MC = multicenter; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PC = placebo-controlled; Pts = patients; RCT = randomized controlled trial; RR = relative risk; TNF-a = tumor necrosis factor-alpha; U.S. = United States; y = years.

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Appendix 1: Search Strategy

Medline search on 8/2/2018 for hidradenitis suppurativa indication review

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

1 exp Hidradenitis Suppurativa/ 1234

2 exp Adalimumab/ 4338

3 1 and 2 69

4 limit 3 to (English language and humans and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 26

Biologics for Autoimmune Diseases

Goal(s):

- Restrict use of biologics to OHP funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Promote use of high value products.

Length of Authorization:

- Up to 12 months

Requires PA:

- All biologics for autoimmune diseases (both pharmacy and physician-administered claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Approved and Funded Indications for Biologic Immunosuppressants.

| Drug Name | Ankylosing Spondylitis | Crohn's Disease | Juvenile Idiopathic Arthritis | Plaque Psoriasis | Psoriatic Arthritis | Rheumatoid Arthritis | Ulcerative Colitis | Other |
|-------------------------------------|------------------------|--|--------------------------------------|------------------|---------------------|----------------------|--------------------|---|
| Abatacept (ORENCIA) | | | ≥2 yo | | ≥18 yo | ≥18 yo | | |
| Adalimumab (HUMIRA) and biosimilars | ≥18 yo | ≥6 yo (Humira) ≥18 yo (biosimilars) | ≥2 yo(Humira) ≥4 yo (biosimilars) | ≥18 yo | ≥18 yo | ≥18 yo | ≥18 yo | Uveitis (non-infectious) ≥18 yo (Humira) |
| Anakinra (KINERET) | | | | | | ≥18 yo | | NOMID |
| Apremilast (OTEZLA) | | | | ≥18 yo | ≥18 yo | | | |
| Baricitinib (LUMIANT) | | | | | | ≥18 yo | | |
| Broadalumab (SILIQ) | | | | ≥18 yo | | | | |
| Canakinumab (ILARIS) | | | ≥2 yo | | | | | FCAS ≥4 yo MWS ≥4 yo TRAPS ≥ 4yo |

| Drug Name | Ankylosing Spondylitis | Crohn's Disease | Juvenile Idiopathic Arthritis | Plaque Psoriasis | Psoriatic Arthritis | Rheumatoid Arthritis | Ulcerative Colitis | Other |
|--|------------------------|-----------------|-------------------------------|--|---------------------|----------------------|--|---|
| | | | | | | | | HIDS ≥ 4 yo MKD ≥ 4 yo FMF ≥ 4 yo |
| Certolizumab (CIMZIA) | ≥18 yo | ≥18 yo | | ≥18 yo | ≥18 yo | ≥18 yo | | |
| Etanercept (ENBREL) and biosimilars | ≥18 yo | | ≥2 yo | ≥4 yo (Enbrel) ≥18 yo (biosimilars) | ≥18 yo | ≥18 yo | | |
| Golimumab (SIMPONI and SIMPONI ARIA) | ≥18 yo | | | | ≥18 yo | ≥18 yo | ≥18 yo (Simponi) | |
| Guselkumab (Tremfya) | | | | ≥18 yo | | | | |
| Infliximab (REMICADE) and biosimilars | ≥18 yo | ≥6 yo | | ≥18 yo | ≥18 yo | ≥18 yo | ≥6 yo (Remicade) ≥18 yo (biosimilars) | |
| Ixekizumab (TALTZ) | | | | ≥18 yo | ≥18 yo | | | |
| Rituximab (RITUXAN) | | | | | | ≥18 yo | | CLL ≥18 yo NHL ≥18 yo GPA ≥18 yo |
| Sarilumab (KEVZARA) | | | | | | ≥18 yo | | |
| Secukinumab (COSENTYX) | ≥18 yo | | | ≥18 yo | ≥18 yo | | | |
| Tildrakizumab-asmn (ILUMYA) | | | | ≥18 yo | | | | |
| Tocilizumab (ACTEMRA) | | | ≥2 yo | | | ≥18 yo | | CRS ≥2 yo GCA ≥18 yo |
| Tofacitinib (XELJANZ) | | | | | ≥18 yo | ≥18 yo | ≥18 yo | |
| Ustekinumab (STELARA) | | ≥ 18 yo | | ≥12 yo | ≥18 yo | | | |
| Vedolizumab (ENTYVIO) | | ≥18 yo | | | | | ≥18 yo | |

Abbreviations: CLL = Chronic Lymphocytic Leukemia; CRS = Cytokine Release Syndrome; FCAS = Familial Cold Autoinflammatory Syndrome; FMF = Familial Mediterranean Fever; GCA = Giant Cell Arteritis; GPA = Granulomatosis with Polyangiitis (Wegener's Granulomatosis); HIDS: Hyperimmunoglobulin D Syndrome; MKD = Mevalonate Kinase Deficiency; MWS = Muckle-Wells Syndrome; NHL = Non-Hodgkin's Lymphoma; NOMID = Neonatal Onset Multi-Systemic Inflammatory Disease; TRAPS = Tumor Necrosis Factor Receptor Associated Periodic Syndrome; yo = years old.

| Approval Criteria | | |
|---|--|--|
| 1. What diagnosis is being treated? | Record ICD-10 code. | |
| 2. Is the diagnosis funded by OHP? | Yes: Go to #3 | No: Pass to RPh. Deny; not funded by the OHP. |
| 3. Is this a request for continuation of therapy? | Yes: Go to Renewal Criteria | No: Go to #4 |
| 4. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product? <u>Message:</u> <ul style="list-style-type: none"> Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics Committee. | Yes: Inform prescriber of preferred alternatives. | No: Go to #5 |
| 5. Has the patient been screened for latent or active tuberculosis and if positive, started tuberculosis treatment? | Yes: Go to #6 | No: Pass to RPh. Deny; medical appropriateness. |

Approval Criteria

| | | |
|---|--|---|
| <p>6. Is the diagnosis Juvenile Idiopathic Arthritis, non-Hodgkin Lymphoma, Chronic Lymphocytic Leukemia, Non-infectious Posterior Uveitis, or one of the following syndromes:</p> <ul style="list-style-type: none">• Familial Cold Autoinflammatory Syndrome• Muckle-Wells Syndrome• Neonatal Onset Multi-Systemic Inflammatory Disease• Tumor Necrosis Factor Receptor Associated Periodic Syndrome• Hyperimmunoglobulin D Syndrome• Mevalonate Kinase Deficiency• Familial Mediterranean Fever• Giant Cell Arteritis• Cytokine Release Syndrome <p>AND</p> <p>Is the request for a drug FDA-approved for one of these conditions as defined in Table 1?</p> | <p>Yes: Approve for length of treatment.</p> | <p>No: Go to #7</p> |
| <p>7. Is the diagnosis ankylosing spondylitis and the request for a drug FDA-approved for this condition as defined in Table 1?</p> | <p>Yes: Go to #8</p> | <p>No: Go to #9</p> |
| <p>8. If the request is for a non-preferred agent, has the patient failed to respond to a Humira® product or an Enbrel® product after a trial of at least 3 months?</p> | <p>Yes: Approve for up to 6 months.</p> <p>Document therapy with dates.</p> | <p>No: Pass to RPh. Deny; medical appropriateness.</p> |

Approval Criteria

| | | |
|--|---|---|
| <p>9. Is the diagnosis plaque psoriasis and the request for a drug FDA-approved for this condition as defined in Table 1?</p> <p>Note: Only treatment for <i>severe</i> plaque psoriasis is funded by the OHP.</p> | <p>Yes: Go to #10</p> | <p>No: Go to #12</p> |
| <p>10. Is the plaque psoriasis severe in nature, which has resulted in functional impairment (e.g., inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) <u>and</u> one or more of the following:</p> <ul style="list-style-type: none"> • At least 10% body surface area involvement; <u>or</u> • Hand, foot or mucous membrane involvement? | <p>Yes: Go to #11</p> | <p>No: Pass to RPh. Deny; not funded by the OHP.</p> |
| <p>11. Has the patient failed to respond to each of the following first-line treatments:</p> <ul style="list-style-type: none"> • Topical high potency corticosteroid (e.g., betamethasone dipropionate 0.05%, clobetasol propionate 0.05%, fluocinonide 0.05%, halcinonide 0.1%, halobetasol propionate 0.05%; triamcinolone 0.5%); <u>and</u> • At least one other topical agent: calcipotriene, tazarotene, anthralin; <u>and</u> • Phototherapy; <u>and</u> • At least one other systemic therapy: acitretin, cyclosporine, or methotrexate; <u>and</u> • One biologic agent: either a Humira[®] product or an Enbrel[®] product for at least 3 months? | <p>Yes: Approve for up to 6 months.</p> <p>Document each therapy with dates.</p> | <p>No: Pass to RPh. Deny; medical appropriateness.</p> |
| <p>12. Is the diagnosis rheumatoid arthritis or psoriatic arthritis and the request for a drug FDA-approved for these conditions as defined in Table 1?</p> | <p>Yes: Go to #13</p> | <p>No: Go to #16</p> |

Approval Criteria

| | | |
|---|--|---|
| <p>13. Has the patient failed to respond to at least one of the following medications:</p> <ul style="list-style-type: none"> • Methotrexate, leflunomide, sulfasalazine or hydroxychloroquine for ≥ 6 months; <u>or</u> • Have a documented intolerance or contraindication to disease-modifying antirheumatic drugs (DMARDs)? AND • Had treatment failure with at least one biologic agent: a Humira[®] product or an Enbrel[®] product for at least 3 months? | <p>Yes: Go to #14</p> <p>Document each therapy with dates.</p> <p>If applicable, document intolerance or contraindication(s).</p> | <p>No: Pass to RPh. Deny; medical appropriateness.</p> |
| <p>14. Is the request for tofacitinib?</p> | <p>Yes: Go to #15</p> | <p>No: Approve for up to 6 months.</p> |
| <p>15. Is the patient currently on other biologic therapy or on a potent immunosuppressant like azathioprine, tacrolimus or cyclosporine?</p> <p><u>Note:</u> Tofacitinib may be used concurrently with methotrexate or other oral DMARD drugs.</p> | <p>Yes: Pass to RPh. Deny; medical appropriateness.</p> | <p>No: Approve for up to 6 months.</p> |
| <p>16. Is the diagnosis Crohn's disease or ulcerative colitis and the request for a drug FDA-approved for these conditions as defined in Table 1?</p> | <p>Yes: Go to #17</p> | <p>No: Go to #18</p> |

Approval Criteria

| | | |
|--|---|---|
| <p>17. Has the patient failed to respond to at least one of the following conventional immunosuppressive therapies for ≥ 6 months:</p> <ul style="list-style-type: none"> • Mercaptopurine, azathioprine, or budesonide; <u>or</u> • Have a documented intolerance or contraindication to conventional therapy? • AND • For Crohn's Disease patients only: has the patient tried and failed a 3 month trial of a Humira[®] product? | <p>Yes: Approve for up to 12 months.</p> <p>Document each therapy with dates.</p> <p>If applicable, document intolerance or contraindication(s).</p> | <p>No: Pass to RPh. Deny; medical appropriateness.</p> |
| <p>18. Is the diagnosis Granulomatosis with Polyangiitis and the requested drug rituximab for <i>induction</i> of remission?</p> | <p>Yes: Approve for length of treatment.</p> | <p>No: Go to #19</p> |
| <p>19. Is the diagnosis Granulomatosis with Polyangiitis and the requested drug rituximab for <i>maintenance</i> of remission?</p> | <p>Yes: Go to #20</p> | <p>No: Pass to RPh. Deny; medical appropriateness.</p> |
| <p>20. Has the patient failed to respond to at least one of the following conventional immunosuppressive therapies for maintenance of remission, in conjunction with a low-dose corticosteroid, for ≥ 6 months:</p> <ul style="list-style-type: none"> • Azathioprine, leflunomide, or methotrexate • Have a documented intolerance or contraindication to DMARDs? | <p>Yes: Approve for up to 12 months.</p> | <p>No: Pass to RPh. Deny; medical appropriateness.</p> |

Renewal Criteria

1. Has the patient's condition improved as assessed by the prescribing physician and physician attests to patient's improvement.

Yes: Approve for 6 months.

Document baseline assessment and physician attestation received.

No: Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: 1/18 (DM; JP); 7/17; 11/16; 9/16; 3/16; 7/15; 9/14; 8/12
Implementation: 3/1/18; 9/1/17; 1/1/17; 9/27/14; 2/21/13

Sacroiliac Joint Dysfunction Prioritization

Question: Should SI joint dysfunction paired with surgical fusion be moved to a higher priority line?

Question source: Andy Kranenburg, MD orthopedic surgeon from Medford; SI-Bone, manufacturer of SI fusion device

Issue: SI joint fusion is a surgical treatment used to address pain that originates from the joint between bones in the spine and hip (sacrum and ilium). The clinical presentation of SI joint pain varies from patient to patient, but buttock pain extending into the posterolateral thigh is the most common pattern. SI joint pain is thought to be the primary source of pain for approximately 10% to 30% of cases of mechanical low back pain. However, estimating an accurate prevalence of SI joint pain is challenging because no universally accepted gold standard for diagnosis exists. The current reference standard for diagnosis is relief of pain after anesthetic SI joint injection. Although diagnosis can be challenging, the impact of SI joint pain on quality of life is significant.

Andy Kranenburg, MD from Medford, testified at the August and October 2018 VBBS meetings regarding the treatment of sacroiliac joint pain and dysfunction. Currently, there is a guideline on the Prioritized List regarding when treatment is appropriate, but the diagnosis is on an uncovered line. He requested reconsideration of the prioritization of sacroiliac joint dysfunction to a line above the funding level.

At the October, 2018 VBBS meeting, Dr. Kranenburg gave a presentation outlining his proposed scoring for SI joint dysfunction. Kranenburg argued that SI joint dysfunction is inappropriately classified as a back condition when it should be categorized as a hip or pelvic condition. The guideline restricting coverage of surgery for back conditions to those with abnormal neurological findings is not appropriate for SI joint conditions. His suggested scoring is shown later in this document.

The discussion amongst VbBS members centered on the need to re-look at the published RCTs to look at the reported effectiveness. It was later identified that the Washington Health Technology Assessment group was doing an evidence review on SI joint fusion and further discussion of this topic was tabled until that review was available.

There has been concern among VBBS members that SI joint fusion had higher levels of adverse events than reported in the literature reviewed to date.

Current Prioritized List status:

ICD-10 M46.1 (Sacroiliitis, not elsewhere classified) and CPT 27279 (Arthrodesis, sacroiliac joint, percutaneous or minimally invasive (indirect visualization), with image guidance, includes obtaining bone graft when performed, and placement of transfixing device) are currently on line 527 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS along with a guideline regarding when fusion should be covered. Sacroiliitis is also on line 401 CONDITIONS OF THE BACK AND SPINE for non-surgical treatments.

Sacroiliac Joint Dysfunction Prioritization

Evidence

Washington HTA 2018, Sacroiliac joint fusion <https://www.hca.wa.gov/assets/program/si-fusion-final-rpt-20181130.pdf>

- 1) N=43 studies
 - a. 8 were controlled studies (2 RCTs and 6 CCSs), 32 were uncontrolled studies, and 3 were cost studies
 - b. All studies included in the VBBS/HERC 2016 review were included in the HTA report except:
 - i. Duhan: article was submitted by the manufacturer
 - ii. **Schoell, 2016** [submitted by Vern Saboe]
 1. Retrospective database study of the nationwide Humana database, specifically looking at harms of SI joint fusion
 2. N = 469 within the Humana insurance database who received minimally invasive SI fusion between 2007 and 2014.
 3. Overall complication rate of 13.2% (n=62) was seen at 90 days postoperatively and 16.4% (n=77) at 6 months.
- 2) Pain, disability, and quality of life
 - a. Two RCTs and 1 CCS compared minimally invasive SI joint fusion surgery using the iFuse Implant System with conservative management and observed larger improvements in a visual analog scale for pain (between-group differences at 6 months based on the RCTs: -40.5 mm [95% CI, -30.9 to -50.1], -38.1 mm [95% CI not reported; P < 0.0001] and at 6 months to 3.5 years based on the CCS: -6 cm [95% CI, not reported; P < 0.001]). These studies also observed larger improvements in physical function measured using the Oswestry Disability Index (ODI) (between-group differences at 6 months based on the RCTs: -25.4 points [95% CI, -18.3 to -32.5] and -19.8 points [95% CI, not reported, P < 0.0001] and at 6 months to 3.5 years: -24 points [95% CI, not reported; P < 0.001]) based on the CCS). We graded these outcomes as moderate quality from the RCTs and very low quality from the CCS.
 - i. Note: the minimal clinically important difference in the visual analog scale for pain is reported to be 20-40 mm (varies by study and condition)
 - ii. Note: minimally clinically important difference (MCID) in the ODI generally found to be 12-15 points. FDA standard for good to excellent surgical outcomes is a change in 15 points on the ODI
 - b. One CCS compared open fusion to no surgery at 11 to 32 years and observed no difference in pain, physical function, or quality of life; we graded these outcomes as very low quality.
 - c. Three CCSs compared minimally invasive fusion with iFuse to open fusion. We graded all outcomes for this comparison as very low quality. One CCS reported larger improvements in pain measured with a visual analog scale (between-group difference over 2 years: -3 cm [95% CI, -2.1 to -4.0]); the other 2 studies did not report pain outcomes but found mixed findings for physical function measured by the ODI. All 3 studies observed significantly shorter hospital length of stay among iFuse recipients compared to open fusion; the range of difference was 1.3 to 3.8 days. All 3 studies reported a similar incidence of adverse events between groups but reported mixed findings for the incidence of revision surgery. One of the 3 studies reported significantly fewer revisions among participants that received iFuse (absolute risk difference [ARD] -

Sacroiliac Joint Dysfunction Prioritization

- 51.3% [95% CI, -60.1% to -42.4%]); the other 2 studies reported infrequent revisions in both the iFuse and the open fusion groups.
- d. One CCS compared minimally invasive fusion with iFuse to minimally invasive fusion with screw fixation; significantly fewer revisions were required among participants who received iFuse (ARD -57.5% [95% CI, -74.8% to -40.2%]). We graded this outcome as very low quality.
- 3) Opioid use
 - a. At 6 months, no change found in percent of opioid use with surgery based on 1 RCT (N=148). Low quality of evidence.
 - b. At 6 months to 3.5 years, significant difference ($P < 0.001$) between groups in oral morphine equivalents used at the time of last follow-up: iFuse (3.1 mg/day), SI denervation (32.2 mg/day), conservative management (38.5 mg/day). Based on 1 CCS (N = 137), very low quality of evidence
 - 4) Cost effectiveness
 - a. One cost-effectiveness study reported a cost per additional quality-adjusted life year gained of \$13,313; we graded this outcome as very low quality.
 - 5) Safety
 - a. Thirty-two uncontrolled studies reported safety outcomes for a variety of open and minimally invasive fusion procedures. We evaluated many as having a high risk of bias; further outcome definition and ascertainment methods varied widely. One study, which used an insurance claims database to identify 469 minimally invasive fusion procedures between 2007 and 2014 reported a 90-day incidence of complications of 13.2%. Another study, which used a post market surveillance database of 11,388 iFuse procedures, reported an incidence of revision surgery of 2.8% over the years 2009 to 2014.
 - 6) **Conclusions:** Among patients meeting diagnostic criteria for SI joint pain or dysfunction and who have not responded adequately to conservative care, minimally invasive SI joint fusion surgery with the iFuse Implant System is more effective than conservative management for reducing pain and improving function, and is likely cost-effective. Minimally invasive SI joint fusion surgery with iFuse is also more effective than open fusion for reducing pain and is associated with a shorter hospital length of stay. Serious adverse events from surgery with iFuse are infrequently reported in controlled studies but may be higher in usual practice based on evidence from uncontrolled studies. The incidence of revision surgery is likely no higher than 3.4% at 2 years. Limited evidence is available that compares open fusion to minimally invasive fusion or that evaluates procedures other than iFuse.

Letter from Dr. Saboe:

There have been three new studies since we last visited this issue, two of which were again funded by the device manufacturer and a third independent. There has also been a review of evidence by our HERC counterparts in Washington State and recommendations that are favorable toward the procedure however, I remain skeptical.

I respectfully suggest that at the very least chiropractic and/or osteopathic manipulative therapy must be added to the list of non-operative treatments listed in our proposed, guideline/medical policy. Those non-operative treatments currently include, "medication optimization," "activity

Sacroiliac Joint Dysfunction Prioritization

modification,” “bracing,” and “active therapeutic exercise targeted at the lumbar spine, pelvis, SIJ and hip including a home exercise program.”

Colleagues and I have been reviewing the medical literature for high quality evidence that supports the efficacy of each of these interventions specifically in regards to the treatment of SIJ dysfunction/pain (not simply, “low back pain”). It appears that the strength of evidence of efficacy for chiropractic and osteopathic manipulative therapy for the treatment of SIJ dysfunction is at least as strong as for the other listed non-operative treatments.

So again, I recommend chiropractic and/or osteopathic manipulative therapy be added to our guideline as one of the non-operative interventions that must have been tried prior to qualifying for minimally invasive sacroiliac joint fusion surgery.

Note from HERC staff: there were no studies of chiropractic manipulation of the SI joint identified in MedLine on a January 7, 2019 search.

Sacroiliac Joint Dysfunction Prioritization

Model Prioritization for Sacroiliac Joint Dysfunction with Surgical Fusion

| | Line 346 | Line 527 | HERC staff proposal | Kranenburg proposal |
|--------------------------------|----------|----------|---------------------|---------------------|
| Category (Non-Fatal Condition) | 7 | 7 | 7 | 7 |
| Healthy Life Years (0-10) | 5 | 4 | 4 | 6 |
| Suffering (0-5) | 4 | 3 | 3 | 5 |
| Population effects (0-5) | 0 | 0 | 0 | 0 |
| Vulnerable population (0-5) | 0 | 0 | 0 | 0 |
| Tertiary prevention (0-5) | 0 | 0 | 0 | 0 |
| Effectiveness (0-5) | 3 | 1 | 4 | 4 |
| Need for service (0-1) | 1 | 0.8 | 0.8 | 1 |
| Net cost | 2 | 2 | 2 | |
| Score | 780 | 112 | 560 | 960 |
| Approximate line | 346 | 527 | 418 | 330 |

Line 346 CONDITIONS OF THE BACK AND SPINE WITH URGENT SURGICAL INDICATIONS

Line 527 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS

Possible similar line:

Line 356 RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, OSTEOCHONDRITIS DISSECANS, AND ASEPTIC NECROSIS OF BONE

Note: line 346 has a guideline requiring neurological damage prior to authorizing surgery. This line would not be appropriate for SI joint fusion

Sacroiliac Joint Dysfunction Prioritization

HERC staff recommendation:

- 1) Create a new line for SI joint fusion as shown below
 - a. Leave ICD-10 M46.1 (Sacroiliitis, not elsewhere classified) on line 527 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS for mild cases
 - b. Leave M46.1 on line 401 CONDITIONS OF THE BACK AND SPINE for medical care
 - c. Chiropractic (CPT 98940- 98942) and osteopathic (CPT 98925- 98929) manipulation will pair on line 401 (medical back line)
- 2) Score as in staff proposal in table above (approximately line 418)
- 3) Modify GN161 as shown below

LINE: XXX

CONDITION: SEVERE SACROILIITIS

TREATMENT: SURGICAL THERAPY

ICD-10: ICD-10 M46.1 (Sacroiliitis, not elsewhere classified)

CPT: 27096 (Injection procedure for sacroiliac joint, anesthetic/steroid, with image guidance (fluoroscopy or CT) including arthrography when performed), 27279 (Arthrodesis, sacroiliac joint, percutaneous or minimally invasive (indirect visualization), with image guidance, includes obtaining bone graft when performed, and placement of transfixing device), 98966-98969, 99051, 99060,99070,99078,99201-99215,99281-99285,99304-99337,99340-99404,99408-99449,99487-99490,99495,99496,99605-99607 (medical office visits, including ER and SNF)

HCPCS: G0260 (Injection procedure for sacroiliac joint; provision of anesthetic, steroid and/or other therapeutic agent, with or without arthrography), G0396-G0397 (alcohol and substance abuse screening), G0463-G0467,G0469,G0470 (FQHC care), G0490, G0511-G0513 (RFQHC care)

GUIDELINE NOTE 161, SACROILIAC ANESTHETIC INJECTIONS AND SACROILIAC JOINT FUSION

Line [XXX](#),527

Sacroiliac joint (SIJ) injection (CPT 20610 and 27096, and HCPCS G0260) is included on [this line](#) [these lines](#) for diagnostic sacroiliac injections with anesthetic only, but not for therapeutic injections or corticosteroid injections. Injections are only covered for patients for whom SIJ fusion surgery is being considered.

SIJ fusion (CPT 27279) is included on [this line](#) [XXX](#) for patients who have all of the following:

- A) Baseline score of at least 30% on the Oswestry Disability Index (ODI)
- B) Undergone and failed a minimum six months of intensive non-operative treatment that must include non-opioid medication optimization and active therapy. Active therapy is defined as activity modification, chiropractic/osteopathic manipulative therapy, bracing, and/or active therapeutic exercise targeted at the lumbar spine, pelvis, SIJ and hip including a home exercise program. Failure of conservative therapy is defined as less than a 50% improvement on the ODI.
- C) Typically unilateral pain that is caudal to the lumbar spine (L5 vertebrae), localized over the posterior SIJ, and consistent with SIJ pain.
- D) Thorough physical examination demonstrating localized tenderness with palpation over the sacral sulcus (Fortin's point, i.e. at the insertion of the long dorsal ligament inferior to the posterior superior iliac spine or PSIS) in the absence of tenderness of similar severity elsewhere (e.g. greater trochanter, lumbar spine, coccyx) and that other obvious sources for their pain do not exist.

Sacroiliac Joint Dysfunction Prioritization

- E) Positive response to at least three of six provocative tests (e.g. thigh thrust test, compression test, Gaenslen's test, distraction test, Patrick's sign, posterior provocation test).
- F) Absence of generalized pain behavior (e.g. somatoform disorder) and generalized pain disorders (e.g. fibromyalgia).
- G) Diagnostic imaging studies that include ALL of the following:
 - 1) Imaging (plain radiographs and a CT or MRI) of the SIJ that excludes the presence of destructive lesions (e.g. tumor, infection), fracture, traumatic sacroiliac joint instability, or inflammatory arthropathy that would not be properly addressed by percutaneous SIJ fusion
 - 2) Imaging of the pelvis (AP plain radiograph) to rule out concomitant hip pathology
 - 3) Imaging of the lumbar spine (CT or MRI) to rule out neural compression or other degenerative condition that can be causing low back or buttock pain
 - 4) Imaging of the SIJ that indicates evidence of injury and/or degeneration
- H) At least 75 percent reduction of pain for the expected duration of two anesthetics (on separate visits each with a different duration of action), and the ability to perform previously painful maneuvers, following an image-guided, contrast-enhanced intra-articular SIJ injection.

[Otherwise, SIJ fusion is included on line 527.](#)



Clinical Study

Postoperative complications in patients undergoing minimally invasive sacroiliac fusion

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Abstract

BACKGROUND CONTEXT: Minimally invasive sacroiliac (SI) joint fusion has become increasingly relevant in recent years as a treatment for SI joint pathology. Previous studies have found minimally invasive SI fusion to be an effective and safe treatment option for chronic SI joint pain. However, these studies have been primarily single-center, case-based, or manufacturer-sponsored investigations, and as such their findings are limited to their sample populations.

PURPOSE: The aim of this study was to investigate the safety of minimally invasive SI fusion using a large nationwide sample group to more accurately identify complication rates of this increasingly popular procedure.

STUDY DESIGN/SETTING: This is a retrospective database study.

PATIENT SAMPLE: The sample includes patients within the orthopedic subset of Humana database who underwent minimally invasive SI fusion between 2007 and 2014.

OUTCOME MEASURES: Complications and novel lumbar and nerve pathology were the outcome measures.

METHODS: Patients undergoing minimally invasive SI fusion from 2007 to 2014 were identified using the Pearl Diver patient record database (Pearl Diver Technologies, West Conshohocken, PA, USA) from the nationwide private insurance provider Humana Inc. This approach provided access to records of over 18 million patients in every major geographic region of the country. Using the

FDA device/drug status: Not applicable.

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Orthopaedics (33,000 shares, 1%, 33,000 options, less than 1% of entity), Osprey (10 shares, 1%, 10 options, less than 1% of entity), Bone Biologics (51,255 shares, 1%, 51,255 options, less than 1% of entity), Curative Biosciences (1,875 shares, 1%, 1875 options, less than 1% of entity), Pearl Diver (25,000 shares, 1%, 25,000 options, less than 1% of entity), outside the submitted work; Board of Directors: North American Spine Society (Non-financial, reimbursement for travel for board meetings, courses, etc.), North American Spine Foundation (Non-financial), Cervical Spine Research Society (Non-financial, reimbursement for travel for board meetings), AOSpine/AO Foundation (Both, 57446.32 honorariums for board position, Paid to the author), outside the submitted work; Fellowship Support: AO Foundation (E, Spine fellowship funding paid to institution, Paid directly to institution/employer), outside the submitted work.

The disclosure key can be found on the Table of Contents and at www.TheSpineJournalOnline.com.

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Section 5.0

Previously Discussed Items

Donor Breast Milk Guideline Edits

Question: Should the Human Donor Breast Milk Guideline be further edited?

Question source: Renae Wentz, MD, HSD

Issue: Dr. Wentz has identified that the guideline as currently written could be construed to not be indicated for any infants, as the clause about “ongoing severe concerns with persistent diarrhea or malabsorption with improvement on breast milk compared to formula” may never be met in the outpatient setting, since infants fragile enough to still be triaged to receive HBM at hospital discharge with BW < 1500g or severe underlying gastrointestinal disease would not remain outpatient with additional ongoing persistent diarrhea/malabsorption.

Prioritized List Status (implemented January 1, 2019)

GUIDELINE NOTE 183 DONOR BREAST MILK FOR HIGH RISK INFANTS

Line 16, 34, 88, 101

Donor breast milk (T2101) is included on these lines for infants up to 6 months of age (adjusted for gestational age) who meet all of the following criteria:

- Low birth weight (<1500g) OR with severe underlying gastrointestinal disease
- Human donor milk was continued through neonatal hospital discharge for a clear medical indication
- Persistent outpatient medical need for human donor breast milk due to ongoing severe concerns with persistent diarrhea or malabsorption with improvement on breast milk compared to formula
- When maternal breast milk is not available, appropriate or sufficient to meet the infant’s needs, despite lactation support for the mother.

Donor human milk may only be obtained through a milk bank with appropriate quality and infection control standards.

Recommendations:

Consider modifying the guideline note to:

GUIDELINE NOTE 183 DONOR BREAST MILK FOR HIGH RISK INFANTS

Line 16, 34, 88, 101

Donor breast milk (T2101) is included on these lines for infants up to 6 months of age (adjusted for gestational age) who meet all of the following criteria:

- Low birth weight (<1500g) OR with severe underlying gastrointestinal disease
- Human donor milk was continued through neonatal hospital discharge for a clear medical indication
- Persistent outpatient medical need for human donor breast milk (such as, but not limited to, ~~due to ongoing severe concerns with~~ persistent

Donor Breast Milk Guideline Edits

diarrhea or malabsorption with improvement on breast milk compared to formula)

- When maternal breast milk is not available, appropriate or sufficient to meet the infant's needs, despite lactation support for the mother.

Donor human milk may only be obtained through a milk bank with ~~appropriate quality and infection control standards~~ [accreditation from the Human Milk Banking Association of North America \(HMBANA\)](#).

Question: Should the guideline on the Diabetes Prevention Program be modified?

Question source: Public Health, HSD, CCO Medical Directors

Issue:

There is currently a Diabetes Prevention Program (DPP) Implementation Workgroup which involves OHA staff and representation from multiple CCOs. As this workgroup is making it through various issues, they have raised a number of concerns for HERC to address.

- 1) Currently, intensive lifestyle counseling for patients with obesity and overweight (with cardiac risk factors) is technically covered on Line 320. However, many OHP patients may not currently be accessing this benefit. In discussions with CCOs about implementing the DPP benefit, they have expressed interest in using DPP interventions in patients who are obese but do not necessarily meet prediabetes criteria as specified in the new DPP guideline. Also, public health has asked about using CDC criteria which allows people to participate in the program who have risk factors, but do not necessarily have lab confirmation of prediabetes. Therefore, there is interest in clarifying that patients with obesity are also eligible for DPP who may not necessarily meet laboratory criteria.
- 2) There was a CCO question about whether history of gestational diabetes needed to be within the prior year or any history of gestational diabetes would be appropriate.
- 3) Additional clarity about pediatric overweight/obesity in the guideline note itself is necessary

Prioritized List Status

Relevant diagnostic codes

| Code | Code Description | Current List Placement |
|--------|---|--|
| E66.01 | Morbid (severe) obesity due to excess calories | 320 OBESITY IN ADULTS AND CHILDREN; OVERWEIGHT STATUS IN ADULTS WITH CARDIOVASCULAR RISK FACTORS 659 MISCELLANEOUS CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY |
| E66.09 | Other obesity due to excess calories | 320 |
| E66.1 | Drug-induced obesity | 320 |
| E66.2 | Morbid (severe) obesity with alveolar hypoventilation | 320 |
| E66.3 | Overweight | 320 |
| E66.8 | Other obesity | 320 |
| E66.9 | Obesity, unspecified | 320 |

| Code | Code Description | Current List Placement |
|--------|---|--|
| R73.03 | Prediabetes | 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS |
| Z68.1 | Body mass index (BMI) 19.9 or less, adult | Informational Diagnosis File |
| Z68.20 | Body mass index (BMI) 20.0-20.9, adult | Informational Diagnosis File |
| Z68.21 | Body mass index (BMI) 21.0-21.9, adult | Informational Diagnosis File |
| Z68.22 | Body mass index (BMI) 22.0-22.9, adult | Informational Diagnosis File |
| Z68.23 | Body mass index (BMI) 23.0-23.9, adult | Informational Diagnosis File |
| Z68.24 | Body mass index (BMI) 24.0-24.9, adult | Informational Diagnosis File |
| Z68.25 | Body mass index (BMI) 25.0-25.9, adult | Informational Diagnosis File |
| Z68.26 | Body mass index (BMI) 26.0-26.9, adult | Informational Diagnosis File |
| Z68.27 | Body mass index (BMI) 27.0-27.9, adult | Informational Diagnosis File |
| Z68.28 | Body mass index (BMI) 28.0-28.9, adult | Informational Diagnosis File |
| Z68.29 | Body mass index (BMI) 29.0-29.9, adult | Informational Diagnosis File |
| Z68.30 | Body mass index (BMI) 30.0-30.9, adult | 320 OBESITY IN ADULTS AND CHILDREN; OVERWEIGHT STATUS IN ADULTS WITH CARDIOVASCULAR RISK FACTORS |
| Z68.31 | Body mass index (BMI) 31.0-31.9, adult | 320 |
| Z68.32 | Body mass index (BMI) 32.0-32.9, adult | 320 |
| Z68.33 | Body mass index (BMI) 33.0-33.9, adult | 320 |
| Z68.34 | Body mass index (BMI) 34.0-34.9, adult | 320 |
| Z68.35 | Body mass index (BMI) 35.0-35.9, adult | 320 |
| Z68.36 | Body mass index (BMI) 36.0-36.9, adult | 320 |
| Z68.37 | Body mass index (BMI) 37.0-37.9, adult | 320 |
| Z68.38 | Body mass index (BMI) 38.0-38.9, adult | 320 |
| Z68.39 | Body mass index (BMI) 39.0-39.9, adult | 320 |
| Z68.41 | Body mass index (BMI) 40.0-44.9, adult | 320 |
| Z68.42 | Body mass index (BMI) 45.0-49.9, adult | 320 |
| Z68.43 | Body mass index (BMI) 50-59.9, adult | 320 |
| Z68.44 | Body mass index (BMI) 60.0-69.9, adult | 320 |
| Z68.45 | Body mass index (BMI) 70 or greater, adult | 320 |
| Z68.51 | Body mass index (BMI) pediatric, less than 5th percentile for age | Diagnostic Workup File (DWF) |
| Z68.52 | Body mass index (BMI) pediatric, 5th percentile to less than 85th percentile for age | Informational Diagnosis File |
| Z68.53 | Body mass index (BMI) pediatric, 85th percentile to less than 95th percentile for age | 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS |
| Z68.54 | Body mass index (BMI) pediatric, greater than or equal to 95th percentile for age | 3 320 |
| Z86.32 | Personal history of gestational diabetes | 1 Pregnancy 3 |

Treatment codes

| | | |
|-------|---|---|
| 0403T | Preventive behavior change, intensive program of prevention of diabetes using a standardized diabetes prevention program curriculum, provided to individuals in a group setting, minimum 60 minutes, per day | Line 3 |
| 0488T | Preventive behavior change, online/electronic intensive program of prevention of diabetes using a standardized diabetes prevention program curriculum, provided to an individual, per 30 days | Line 3 |
| 99411 | Preventive medicine counseling and/or risk factor reduction intervention(s) provided to individuals in a group setting (separate procedure); approximately 30 minutes | On >500 lines, including line 320. |
| 99412 | Group prevention counseling | On >500 lines, including line 320. |
| 98962 | Education and training for patient self-management by a qualified, nonphysician health care professional using a standardized curriculum, face-to-face with the patient (could include caregiver/family) each 30 minutes; 5-8 patients | 1 Pregnancy 8 Type1 DM 27 Type 2 DM |
| 98969 | Online assessment and management service provided by a qualified nonphysician health care professional to an established patient or guardian, not originating from a related assessment and management service provided within the previous 7 days, using the Internet or similar electronic communications network | On >600 lines, including line 320 |

| | | |
|-------|--|--------|
| G9873 | First Medicare Diabetes Prevention Program (MDPP) core session was attended by an MDPP beneficiary under the MDPP Expanded Model (EM). A core session is an MDPP service that: (1) is furnished by an MDPP supplier during months 1 through 6 of the MDPP services period; (2) is approximately 1 hour in length; and (3) adheres to a CDC-approved DPP curriculum for core sessions | Line 3 |
| G9874 | Four total Medicare Diabetes Prevention Program (MDPP) core sessions were attended by an MDPP beneficiary under the MDPP Expanded Model (EM). A core session is an MDPP service that: (1) is furnished by an MDPP supplier during months 1 through 6 of the MDPP services period; (2) is approximately 1 hour in length; and (3) adheres to a CDC-approved DPP curriculum for core sessions. | Line 3 |
| G9875 | Nine total Medicare Diabetes Prevention Program (MDPP) core sessions were attended by an MDPP beneficiary under the MDPP Expanded Model (EM). A core session is an MDPP service that: (1) is furnished by an MDPP supplier during months 1 through 6 of the MDPP services period; (2) is approximately 1 | Line 3 |

| | | |
|-------|---|--------|
| | hour in length; and (3) adheres to a CDC-approved DPP curriculum for core sessions | |
| G9876 | Two Medicare Diabetes Prevention Program (MDPP) core maintenance sessions (MS) were attended by an MDPP beneficiary in months (mo) 7-9 under the MDPP Expanded Model (EM). A core maintenance session is an MDPP service that: (1) is furnished by an MDPP supplier during months 7 through 12 of the MDPP services period; (2) is approximately 1 hour in length; and (3) adheres to a CDC-approved DPP curriculum for maintenance sessions. The beneficiary did not achieve at least 5% weight loss (WL) from his/her baseline weight, as measured by at least one in-person weight measurement at a core maintenance session in months 7-9. | Line 3 |
| G9877 | Two Medicare Diabetes Prevention Program (MDPP) core maintenance sessions (MS) were attended by an MDPP beneficiary in months (mo) 10-12 under the MDPP Expanded Model (EM). A core maintenance session is an MDPP service that: (1) is furnished by an MDPP supplier during months 7 through 12 of the MDPP services period; (2) is approximately 1 hour in length; and (3) adheres to a CDC-approved DPP curriculum for maintenance sessions. The beneficiary did not achieve at least 5% weight loss (WL) from his/her baseline weight, as measured by at least one in-person weight measurement at a core maintenance session in months 10-12. | Line 3 |
| G9878 | Two Medicare Diabetes Prevention Program (MDPP) core maintenance sessions (MS) were attended by an MDPP beneficiary in months (mo) 7-9 under the MDPP Expanded Model (EM). A core maintenance session is an MDPP service that: (1) is furnished by an MDPP supplier during months 7 through 12 of the MDPP services period; (2) is approximately 1 hour in length; and (3) adheres to a CDC-approved DPP curriculum for maintenance sessions. The beneficiary achieved at least 5% weight loss (WL) from his/her baseline weight, as measured by at least one in-person weight measurement at a core maintenance session in months 7-9. | Line 3 |
| G9879 | Two Medicare Diabetes Prevention Program (MDPP) core maintenance sessions (MS) were attended by an MDPP beneficiary in months (mo) 10-12 under the MDPP Expanded Model (EM). A core maintenance session is an MDPP service that: (1) is furnished by an MDPP supplier during months 7 through 12 of the MDPP services period; (2) is approximately 1 hour in length; and (3) adheres to a CDC-approved DPP curriculum for maintenance sessions. The beneficiary achieved at least 5% weight loss (WL) from his/her baseline weight, as measured by at least one in-person weight measurement at a core maintenance session in months 10-12 | Line 3 |
| G9880 | The MDPP beneficiary achieved at least 5% weight loss (WL) from his/her baseline weight in months 1-12 of the MDPP services period under the MDPP Expanded Model (EM). This is a one-time payment available when a beneficiary first achieves at least 5% weight loss from baseline as measured by an in-person weight measurement at a core session or core maintenance session. | Line 3 |

| | | |
|-------|--|-----------|
| G9881 | The MDPP beneficiary achieved at least 9% weight loss (WL) from his/her baseline weight in months 1-24 under the MDPP Expanded Model (EM). This is a one-time payment available when a beneficiary first achieves at least 9% weight loss from baseline as measured by an in-person weight measurement at a core session, core maintenance session, or ongoing maintenance session. | Line 3 |
| G9882 | Two Medicare Diabetes Prevention Program (MDPP) ongoing maintenance sessions (MS) were attended by an MDPP beneficiary in months (mo) 13-15 under the MDPP Expanded Model (EM). An ongoing maintenance session is an MDPP service that: (1) is furnished by an MDPP supplier during months 13 through 24 of the MDPP services period; (2) is approximately 1 hour in length; and (3) adheres to a CDC-approved DPP curriculum for maintenance sessions. The beneficiary maintained at least 5% weight loss (WL) from his/her baseline weight, as measured by at least one in-person weight measurement at an ongoing maintenance session in months 13-15. | Line 3 |
| G9883 | Two Medicare Diabetes Prevention Program (MDPP) ongoing maintenance sessions (MS) were attended by an MDPP beneficiary in months (mo) 16-18 under the MDPP Expanded Model (EM). An ongoing maintenance session is an MDPP service that: (1) is furnished by an MDPP supplier during months 13 through 24 of the MDPP services period; (2) is approximately 1 hour in length; and (3) adheres to a CDC-approved DPP curriculum for maintenance sessions. The beneficiary maintained at least 5% weight loss (WL) from his/her baseline weight, as measured by at least one in-person weight measurement at an ongoing maintenance session in months 16-18. | Line 3 |
| G9884 | Two Medicare Diabetes Prevention Program (MDPP) ongoing maintenance sessions (MS) were attended by an MDPP beneficiary in months (mo) 19-21 under the MDPP Expanded Model (EM). An ongoing maintenance session is an MDPP service that: (1) is furnished by an MDPP supplier during months 13 through 24 of the MDPP services period; (2) is approximately 1 hour in length; and (3) adheres to a CDC-approved DPP curriculum for maintenance sessions. The beneficiary maintained at least 5% weight loss (WL) from his/her baseline weight, as measured by at least one in-person weight measurement at an ongoing maintenance session in months 19-21. | Line 3 |
| G9885 | Two Medicare Diabetes Prevention Program (MDPP) ongoing maintenance sessions (MS) were attended by an MDPP beneficiary in months (mo) 22-24 under the MDPP Expanded Model (EM). An ongoing maintenance session is an MDPP service that: (1) is furnished by an MDPP supplier during months 13 through 24 of the MDPP services period; (2) is approximately 1 hour in length; and (3) adheres to a CDC-approved DPP curriculum for maintenance sessions. The beneficiary maintained at least 5% weight loss (WL) from his/her baseline weight, as measured by at least one in-person weight measurement at an ongoing maintenance session in months 22-24. | Line 3 |
| G9890 | Bridge Payment: A one-time payment for the first Medicare Diabetes Prevention Program (MDPP) core session, core maintenance session, or ongoing maintenance session furnished by an MDPP supplier to an MDPP beneficiary during months 1-24 of the MDPP Expanded Model (EM) who has previously | Line 3 |

| | | |
|-------|---|--------|
| | received MDPP services from a different MDPP supplier under the MDPP Expanded Model. A supplier may only receive one bridge payment per MDPP beneficiary. | |
| G9891 | MDPP session reported as a line-item on a claim for a payable MDPP Expanded Model (EM) HCPCS code for a session furnished by the billing supplier under the MDPP Expanded Model and counting toward achievement of the attendance performance goal for the payable MDPP Expanded Model HCPCS code.(This code is for reporting purposes only). | Line 3 |

Line: 3

Condition: PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS (See Coding Specification Below) (See Guideline Notes 1,17,64,65,106,122,140,179,181)

Treatment: MEDICAL THERAPY

ICD-10: R73.03,Z00.00-Z00.01,Z00.110-Z00.5,Z00.70-Z00.8,Z01.00-Z01.10,Z01.110-Z01.118,Z01.411-Z01.42,Z08,Z11.1-Z11.4,Z11.51,Z12.11,Z12.2,Z12.31,Z12.4,Z13.1,Z13.220,Z13.31-Z13.39,Z13.41-Z13.6,Z13.820,Z13.88,Z20.1-Z20.7,Z20.810-Z20.89,Z23,Z29.11-Z29.12,Z29.14,Z29.8,Z39.1,Z68.53-Z68.54,Z71.41,Z71.7,Z76.1-Z76.2,Z80.0,Z80.41,Z86.32,Z87.891,Z91.81

CPT: 0403T,0488T,44392,44394,45333,45338,45384,45385,76706,77067,90378,90460-90472,90620,90621,90630-90689,90696-90716,90723-90736,90739-90748,90750,90756,92002-92014,92551,93792,93793,96110,96127,96150-96161,98962-98969,99051,99060,99070,99078,99173,99188,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99451,99452,99487-99491,99495-99498,99605-99607

HCPCS: D0191,D1206,G0008-G0010,G0068,G0071,G0104,G0105,G0121,G0248-G0250,G0296,G0297,G0396,G0397,G0438-G0445,G0463-G0468,G0490,G0511,G0513,G0514,G2010-G2012,G9873-G9891,H0049,H0050,S0285,S0610-S0613,S9443

CPT code 96110 can be billed in addition to other CPT codes, such as evaluation and management (E&M) codes or preventive visit codes.

Line: 320

Condition: OBESITY IN ADULTS AND CHILDREN; OVERWEIGHT STATUS IN ADULTS WITH CARDIOVASCULAR RISK FACTORS (See Guideline Notes 5,8,64,65)

Treatment: BEHAVIORAL INTERVENTIONS INCLUDING INTENSIVE NUTRITIONAL AND PHYSICAL ACTIVITY COUNSELING; BARIATRIC SURGERY

ICD-10: E66.01-E66.9,Z46.51,Z68.30-Z68.45,Z68.54,Z71.3,Z71.82

CPT: 43644,43645,43771-43775,43846-43848,93792,93793,96150-96155,97802-97804,98966-98969,99051,99060,99070,99078,99201-99215,99281-99285,99341-99378,99381-99404,99408-99449,99451,99452,99487-99491,99495-99498

HCPCS: G0068,G0071,G0248-G0250,G0270,G0271,G0396,G0397,G0447,G0463-G0467,G0473,G0490,G0511,G0513,G0514,G2010-G2012,S2083

GUIDELINE NOTE 5, OBESITY AND OVERWEIGHT

Line 320

Medical treatment of overweight (with known cardiovascular risk factors) and obesity in adults is limited to intensive counseling on nutrition and physical activity, provided by health care professionals. Intensive

counseling is defined as face-to-face contact more than monthly. A multidisciplinary team is preferred, but a single clinician could also deliver intensive counseling in primary care or other settings.

Intensive counseling visits are included on this line for 6 months. Intensive counseling visits may continue for an additional 6 months (up to 12 months) as long as there is evidence of continued weight loss or improvement in cardiovascular risk factors based on the intervention. Maintenance visits at the conclusion of the intensive treatment are included on this line no more than monthly after this intensive counseling period. The characteristics of effective behavioral interventions include: high intensity programs; multicomponent (including at a minimum diet and exercise), group-based commercial programs; Mediterranean diet; and the following sub-elements -- calorie counting, contact with a dietician, and comparison to peers.

Known cardiovascular risk factors in overweight persons for which this therapy is effective include: hypertension, dyslipidemia, prediabetes, or the metabolic syndrome. Treatment of prediabetes with the Diabetes Prevention Program (DPP) is addressed on Line 3 in Guideline Note 179.

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

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

GUIDELINE NOTE 179, DIABETES PREVENTION PROGRAM

Line 3

Prediabetes (R73.03) and personal history of gestational diabetes (Z86.32) are included on this line only for the Diabetes Prevention Program (DPP). The only programs included are CDC-recognized lifestyle change programs for DPP.

To be eligible for referral to a CDC-recognized lifestyle change program, patients must meet the following requirements:

- Be at least 18 years old and
- Be overweight (body mass index ≥ 25 ; ≥ 23 if Asian) and
- Have no previous diagnosis of type 1 or type 2 diabetes and
- Not have end-stage renal disease and
- Have a blood test result in the prediabetes range within the past year:
 - Hemoglobin A1C: 5.7%–6.4% or
 - Fasting plasma glucose: 100–125 mg/dL or
 - Two-hour plasma glucose (after a 75 gm glucose load): 140–199 mg/dL or
 - Be previously diagnosed with gestational diabetes

HERC Staff Summary

The Diabetes Prevention Program (DPP) is currently actively being made available to OHP members, however, patients with obesity but not prediabetes currently have limited access to the covered intensive lifestyle treatment. CCOs are interested in having

this streamlined benefit across obese and prediabetic populations. DPP would be an appropriate form of intensive lifestyle treatment. Aligning the obesity line and DPP coverage will improve access and clarify HERC intent to cover intensive lifestyle treatment for obesity, as well as make the benefit easier for CCOs to administer.

HERC Staff Recommendations:

- 1) Enable DPP to also be provided as an alternative to intensive lifestyle counseling on Line 320 (obese patients and overweight with risk factors excluding prediabetes)
- 2) **Code changes**
 - a. Add DPP codes to the obesity line 320
 - i. Add G9873 – G9885, and G9890-G9891
 - ii. Add 0403T and 0488T
 - b. Remove Z68.53-Z68.54 from Line 3 for pediatric overweight/obesity (i.e. for 18-19 year olds). Place on line 320.
 - i. Rationale: Prediabetes or history of gestational diabetes would be the primary diagnosis code, the other obesity codes are not on Line 3.
 - c. Add Z68.25- Z68.29 (overweight BMI codes) to Line 320
 - i. Advise HSD to remove from informational file
 - d. Remove E66.01 Morbid (severe) obesity due to excess calories from line 659
 - i. Rationale: this seems like a relic

3) Modify the DDP Guideline Note as follows

GUIDELINE NOTE 179 DIABETES PREVENTION PROGRAM

Line 3

Prediabetes (R73.03) and personal history of gestational diabetes (Z86.32) are included on this line only for the Diabetes Prevention Program (DPP). The only programs included are CDC-recognized lifestyle change programs for DPP.

To be eligible for referral to a CDC-recognized lifestyle change program, patients must meet the following requirements:

- 1) Be at least 18 years old and
- 2) Be overweight (body mass index ≥ 25 ; ≥ 23 if Asian; [BMI percentile \$\geq 85^{\text{th}}\$ percentile for 18-19 years old](#)) and
- 3) Have no previous diagnosis of type 1 or type 2 diabetes and
- 4) Not have end-stage renal disease and
- 5) Have a blood test result in the prediabetes range within the past year:
 - a. Hemoglobin A1C: 5.7%–6.4% or
 - b. Fasting plasma glucose: 100–125 mg/dL or
 - c. Two-hour plasma glucose (after a 75 gm glucose load): 140–199 mg/dL OR
 - d. [Have a previous diagnosis of](#) gestational diabetes

**4) Modify the Obesity and Overweight Guideline Note 5 as follows:
GUIDELINE NOTE 5, OBESITY AND OVERWEIGHT**

Line 320

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

Intensive counseling visits are included on this line for 6 months. Intensive counseling visits may continue for an additional 6 months (up to 12 months) as long as there is evidence of continued weight loss or improvement in cardiovascular risk factors based on the intervention.

Maintenance visits at the conclusion of the intensive treatment are included on this line no more than monthly after this intensive counseling period. The characteristics of effective behavioral interventions include: high intensity programs; multicomponent (including at a minimum diet and exercise), group-based commercial programs; Mediterranean diet; and the following sub-elements -- calorie counting, contact with a dietician, and comparison to peers.

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

Treatment of prediabetes with the Diabetes Prevention Program (DPP) is addressed on Line 3 in Guideline Note 179. [The DPP program can be used as an alternative to the intensive counseling as above, even in the absence of prediabetes as required by Guideline Note 179.](#)

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

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

Section 6.0

New Discussion Items

Failure to Thrive in Children

Question: Should the ICD-10 code for failure to thrive in children (R62.51) be added to the Prioritized List to allow for pairing with treatments?

Question sources: various providers and CCOs, Hearings Division

Issue: Failure to thrive (child) (ICD-10 R62.51) is currently on the Diagnostic Procedures File. Codes in the “R” region of ICD10 are generally signs and symptoms. Failure to thrive needs diagnostic testing, such as labs or radiologic studies, to rule out various causes. However, when no cause is identified, “failure to thrive” is frequently used as a diagnosis to allow hospitalization for observed feeding (to rule out social causes), and for other treatments. Multiple hospitalizations using this code have apparently been denied in recent years, as well as procedures such as G tube placement. ICD10 P92.6 (Failure to thrive in newborn) is on line 18 FEEDING PROBLEMS IN NEWBORNS.

Failure to thrive in a child is defined as ‘lack of expected normal physical growth’ or ‘failure to gain weight’. Common causes of failure to thrive in children are malnutrition secondary to psychosocial and caregiver factors, child abuse or neglect, malabsorption due to various GI conditions, and congenital or chronic medical conditions. Common treatments when no specific cause is identified might be special formula, feeding consultation, lactation support, PT/OT, etc. When a specific cause is identified (e.g. Crohn’s disease, congenital heart disease), then that diagnosis can be used, and should pair with appropriate treatments on the Prioritized List.

Other payer policies

- 1) Aetna 2018: lists R62.51 as an acceptable diagnosis for use with treatments such as speech therapy, feeding clinic visits, psychotherapy, and medical nutrition therapy
- 2) Regence BCBS 2018: lists R62.51 as an acceptable diagnosis for pairing with various therapies

HERC staff recommendation:

- 1) Add ICD10 R62.51 to line 71 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES
 - a. Allows hospital care, office visits, feeding clinic visits, PT/OT and G tube placement

Procalcitonin

Question: Should procalcitonin be removed from Line 660 and added to the Diagnostic Procedures File?

Question source: HERC Staff

Issue: Procalcitonin was last reviewed in December 2009 and was placed on the Never Covered File as a new CPT code. It has subsequently moved to Line 660 based on insufficient evidence of effectiveness. In recent years there has been a dramatic upsurge in use of procalcitonin based on its proposed ability to help distinguish bacterial infections in the setting of acute illness. It is an inexpensive test (~\$25).

Current Prioritized List Status

| Code | Code Description | Current Line Placement |
|-------|---------------------|--|
| 84145 | Procalcitonin (PCT) | 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS |

Evidence Summary:

Shuetz, 2017

<https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD007498.pub3/full>

1. Cochrane systematic review of procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections
2. 32 eligible RCTs, individual participant data from 26 trials including 6708 participants contributed to individual level meta-analysis
3. Results:
 - a. Lower mortality - There were 286 deaths in 3336 procalcitonin-guided participants (8.6%) compared to 336 in 3372 controls (10.0%), (adjusted OR 0.83, 95% CI 0.70 to 0.99, P = 0.037). [although couldn't look at primary care trials]
 - b. No difference in treatment failure - procalcitonin-guided participants (23.0% versus 24.9% in the control group, adjusted OR 0.90, 95% CI 0.80 to 1.01, P = 0.068).
 - c. Reduction in antibiotic exposure and side effects - procalcitonin guidance was associated with a 2.4-day reduction in antibiotic exposure (5.7 versus 8.1 days, 95% CI -2.71 to -2.15, P < 0.001) and lower risk of antibiotic-related side effects (16.3% versus 22.1%, adjusted OR 0.68, 95% CI 0.57 to 0.82, P < 0.001).
 - d. No difference in length of hospital stay and intensive care unit stay

Procalcitonin

4. Conclusions: The use of procalcitonin to guide initiation and duration of antibiotic treatment results in lower risks of mortality, lower antibiotic consumption, and lower risk for antibiotic-related side effects in patients with acute respiratory infections.

Huang, 2017

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5700008/pdf/13613_2017_Article_338.pdf

1. Systematic review and metanalysis of procalcitonin to guide antibiotic therapy in the ICU setting
2. 13 trials enrolling 5136 patients. These studies used PCT in three clinical strategies: initiation, discontinuation, or combination of antibiotic initiation and discontinuation strategies.
3. Pooled analysis showed a PCT-guided antibiotic discontinuation strategy had fewer total days with antibiotics (MD - 1.66 days; 95% CI - 2.36 to - 0.96 days), longer antibiotic-free days (MD 2.26 days; 95% CI 1.40-3.12 days), and lower short-term mortality (RR 0.87; 95% CI 0.76-0.98), without adversely affecting other outcomes. Only a few studies reported data on other PCT-guided strategies for antibiotic therapies, and the pooled results showed no benefit in the predefined outcomes.
4. Conclusions: our meta-analysis produced evidence that among all the PCT-based strategies, only using PCT for antibiotic discontinuation can reduce both antibiotic exposure and short-term mortality in a critical care setting.

Andriolo, 2017

<https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010959.pub2/full>

1. Cochrane systematic review of procalcitonin evaluation for reducing mortality in adults with sepsis, severe sepsis or septic shock
2. 10 trials with 1215 participants.
3. Low-quality evidence showed no significant differences in mortality at longest follow-up (risk ratio (RR) 0.81, 95% confidence interval (CI) 0.65 to 1.01; $I^2 = 10\%$; 10 trials; N = 1156), at 28 days (RR 0.89, 95% CI 0.61 to 1.31; $I^2 = 0\%$; four trials; N = 316), at ICU discharge (RR 1.03, 95% CI 0.50 to 2.11; $I^2 = 49\%$; three trials; N = 506) and at hospital discharge (RR 0.98, 95% CI 0.75 to 1.27; $I^2 = 0\%$; seven trials; N = 805; moderate-quality evidence). However, mean time receiving antimicrobial therapy in the intervention groups was -1.28 days (95% CI to -1.95 to -0.61; $I^2 = 86\%$; four trials; N = 313; very low-quality evidence). No primary study has analysed the change in antimicrobial regimen from a broad to a narrower spectrum.

Procalcitonin

4. Authors' conclusions: Up-to-date evidence of very low to moderate quality, with insufficient sample power per outcome, does not clearly support the use of procalcitonin-guided antimicrobial therapy to minimize mortality, mechanical ventilation, clinical severity, reinfection or duration of antimicrobial therapy of patients with septic conditions.

Westwood, 2015 <https://www.ncbi.nlm.nih.gov/books/NBK327098/>

1. Systematic review and cost-effectiveness of procalcitonin in the Emergency Department
2. 18 studies (36 reports) were included in the systematic review. All but one of the ED studies were in patients with respiratory symptoms.
3. PCT algorithms were associated with reduced antibiotic duration [WMD -3.19 days, 95% confidence interval (CI) -5.44 to -0.95 days, I (2) = 95.2%; four studies], hospital stay (WMD -3.85 days, 95% CI -6.78 to -0.92 days, I (2) = 75.2%; four studies) and a trend towards reduced intensive care unit (ICU) stay (WMD -2.03 days, 95% CI -4.19 to 0.13 days, I (2) = 81.0%; four studies). PCT algorithms were associated with a reduction in the proportion of adults (RR 0.77, 95% CI 0.68 to 0.87; seven studies) and children (RR 0.86, 95% CI 0.80 to 0.93) receiving antibiotics, reduced antibiotic duration (two studies).
4. There were no differences for adverse clinical outcomes.
5. PCT testing was cost-saving for (1) adults with confirmed or highly suspected sepsis in an ICU setting; (2) adults with suspected bacterial infection presenting to the ED; and (3) children with suspected bacterial infection presenting to the ED.
6. Conclusions: the limited available data suggest that PCT testing may be effective and cost-effective when used to guide discontinuation of antibiotics in adults being treated for suspected or confirmed sepsis in ICU settings and initiation of antibiotics in adults presenting to the ED with respiratory symptoms and suspected bacterial infection.

Procalcitonin

HERC Staff Summary

Procalcitonin is a commonly used test to determine the need for antibiotics in Emergency Departments and ICU settings, and, in acute respiratory conditions, appears to be associated with a mortality benefit and fewer unnecessary antibiotic days.

Recommendations:

- 1) Delete 84145 Procalcitonin from Line 660, removing the entry in Guideline Note 173
- 2) Recommend HSD add 84145 to the Diagnostic Procedures File

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 660

The following Interventions are prioritized on Line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

| | | | |
|-------|---------------------|--|---------------|
| 84145 | Procalcitonin (PCT) | Insufficient evidence of effectiveness | December 2009 |
|-------|---------------------|--|---------------|

Fecal Calprotectin

Question: Should fecal calprotectin (CPT 83993) be moved to a covered line or the Diagnostic List?

Question source: Alison Little, CCO medical director

Issue: Fecal calprotectin is currently on line 660/GN173, but no rationale for this listing is given. No mention was found in any minutes regarding why this CPT code was added to the Excluded List. Dr. Little is requesting that it be considered for coverage, as “it is used in monitoring inflammatory bowel disease, and...is not expensive.”

The main diseases that cause an increased excretion of fecal calprotectin are inflammatory bowel diseases, coeliac disease, infectious colitis, necrotizing enterocolitis, intestinal cystic fibrosis and colorectal cancer. Fecal calprotectin is regularly used as an indicator for inflammatory bowel diseases (IBD) during treatment and as a diagnostic marker. Inflammatory processes result in an influx of neutrophils into the bowel lumen. Since calprotectin comprises as much as 60% of the soluble protein content of the cytosol of neutrophils, it can serve as a marker for the level of intestinal inflammation.

Fecal calprotectin testing has been proposed as a noninvasive test to diagnose inflammatory bowel disease (IBD). Other potential uses are to evaluate response to treatment for patients with IBD and as a marker of relapse. Fecal calprotectin testing has been used to distinguish between organic and functional intestinal disease.

Evidence

- 1) **Holtman 2016**, systematic review and meta-analysis of fecal calprotectin in pediatric inflammatory bowel disease
<http://pediatrics.aappublications.org/content/pediatrics/137/1/e20152126.full.pdf>
 - a. N=19 studies (N=2806), all appear to be case control or cohort
 - b. Symptoms (abdominal pain, diarrhea, rectal bleeding, and weight loss) had pooled sensitivities ranging from 0.48 to 0.82 and specificities ranging from 0.17 to 0.78.
 - c. Of all the blood markers, C-reactive protein (CRP) (9 studies) and albumin (6 studies) had the best performance, with pooled sensitivities of 0.63 (0.51–0.73) and 0.48 (0.31–0.66), respectively, and specificities of 0.88 (0.80–0.93) and 0.94 (0.86–0.98).
 - d. Assessment of fecal calprotectin (FCal) (10 studies) had a pooled sensitivity of 0.99 (0.92–1.00) and a specificity of 0.65 (0.54–0.74). One limitation was that none of the studies was conducted in nonreferred children.
 - e. **CONCLUSIONS:** In children whose pediatrician is considering an endoscopy, symptoms are not accurate enough to identify low-risk patients in whom an endoscopy can be avoided. FCal, CRP, and albumin findings are potentially of clinical value, given their ability to select children at low risk (negative FCal test result) or high risk (positive CRP or albumin test result) for IBD.
- 2) **Kostakis 2013**, systematic review of fecal calprotectin in diagnosing pediatric inflammatory bowel disease
 - a. N=34 studies, appeared to be case control or cohort studies
 - b. Fecal calprotectin levels of patients with inflammatory bowel disease are much higher than those of healthy controls or patients with functional disorders or other gastrointestinal diseases.
 - c. High sensitivity and positive likelihood ratio, low negative likelihood ratio, but moderate specificity.

Fecal Calprotectin

- d. 50 lg/g seems to be the most proper cutoff point for the fecal calprotectin test.
 - e. Conclusions: The fecal calprotectin test could be used for supporting diagnosis or confirming relapse of inflammatory bowel disease in pediatric patients. A positive result could confirm the suspicion of either inflammatory bowel disease diagnosis or inflammatory bowel disease relapse, due to the high sensitivity of the test, but a negative result should not exclude these conditions, due to its moderate specificity.
- 3) **Van Rheenen 2012**, systematic review and meta-analysis of fecal calprotectin for diagnosing inflammatory bowel disease in children, adolescents, and adults
<https://www.bmj.com/content/bmj/341/bmj.c3369.full.pdf>
- a. N=13 studies
 - i. N=6 in adults (670 patients)
 - ii. N=7 in children and teenagers (371 patients)
 - b. Inflammatory bowel disease was confirmed by endoscopy in 32% (n=215) of the adults and 61% (n=226) of the children and teenagers. In the studies of adults, the pooled sensitivity and pooled specificity of calprotectin was 0.93 (95% confidence interval 0.85 to 0.97) and 0.96 (0.79 to 0.99) and in the studies of children and teenagers was 0.92 (0.84 to 0.96) and 0.76 (0.62 to 0.86).
 - c. Screening by measuring faecal calprotectin levels would result in a 67% reduction in the number of adults requiring endoscopy. The downside of this screening strategy is delayed diagnosis in 6% of adults because of a false negative test result.
 - d. In the population of children and teenagers, 65 instead of 100 would undergo endoscopy. Nine of them will not have inflammatory bowel disease, and diagnosis will be delayed in 8% of the affected children.
 - e. Conclusion: Testing for faecal calprotectin is a useful screening tool for identifying patients who are most likely to need endoscopy for suspected inflammatory bowel disease. The discriminative power to safely exclude inflammatory bowel disease was significantly better in studies of adults than in studies of children.
- 4) **Mao 2012**, systematic review and meta-analysis of fecal calprotectin for predicting relapse of inflammatory bowel disease
- a. N=6 studies (672 patients), prospective cohort or case control
 - b. The pooled sensitivity and specificity of fecal calprotectin (FC) to predict relapse of quiescent IBD was 78% (95% confidence interval [CI]: 72–83) and 73% (95% CI: 68–77), respectively. The area under the summary receiver-operating characteristic (sROC) curve was 0.83 and the diagnostic odds ratio was 10.31 (95% CI: 5.05–21.06). The capacity of FC to predict relapse was comparable between ulcerative colitis (UC) and Crohn's disease (CD).
 - c. Conclusions: As a simple and noninvasive marker, FC is useful to predict relapse in quiescent IBD patients.

Cost effectiveness

- 1) **Yang 2014**, cost effectiveness of fecal calprotectin in diagnosis of IBD
- a. In adults, FC screening saved \$417/patient but delayed diagnosis for 2.2/32 patients with IBD, among 100 screened patients. In children, FC screening saved \$300/patient but delayed diagnosis for 4.8/61 patients with IBD, among 100 screened patients. If endoscopic biopsy analysis remained the standard for diagnosis, direct endoscopic evaluation would cost an additional \$18,955 in adults and \$6,250 in children to avoid 1 false negative result from FC screening. Sensitivity analyses showed that cost effectiveness of FC screening varied with the sensitivity of the test and the pre-test

Fecal Calprotectin

probability of IBD in adults and children. Pre-test probabilities for IBD of $\leq 75\%$ in adults and $\leq 65\%$ in children made FC screening cost-effective, but cost ineffective if the probabilities were $\geq 85\%$ and $\geq 78\%$ in adults and children, respectively.

- b. **CONCLUSIONS**—Screening adults and children to measure fecal levels of calprotectin is effective and cost-effective in identifying those with IBD on a per-case basis when the pretest probability is $\leq 75\%$ for adults and $\leq 65\%$ for children. The utility of the test is greater for adults than children. Increasing the FC cut-off level to $\geq 50 \mu\text{g/g}$ increases diagnostic accuracy without substantially increasing total cost.

Expert guidelines

- 1) *American College of Gastroenterology* <http://gi.org/wp-content/uploads/2018/04/ajg201827.pdf>

- a. Management of Crohn's disease in adults guideline, 2018
 - i. Diagnosis of adults:
 1. In patients who have symptoms of active Crohn's disease, stool testing should be performed to include fecal pathogens, *Clostridium difficile* testing, and may include studies that identify gut inflammation such as a fecal calprotectin.
 2. Fecal calprotectin is a helpful test that should be considered to help differentiate the presence of IBD from irritable bowel syndrome (IBS) (strong recommendation, moderate level of evidence).
 - ii. Monitoring disease activity:
 1. Fecal calprotectin and fecal lactoferrin measurements may have an adjunctive role in monitoring disease activity.
 2. Levels of $>100 \mu\text{g/g}$ indicate endoscopic recurrence with a sensitivity in the range of 89%. In patients with an infliximab-induced remission, fecal calprotectin of $>160 \mu\text{g/g}$ has a sensitivity of 91.7% and a specificity of 82.9% to predict relapse.
- b. Management of ulcerative colitis in adults, 2010
 - i. Calprotectin not mentioned
 - ii. Currently guideline is under revision

Other policies:

Wellmark BCBS 2017: experimental

Aetna 2018: Aetna considers fecal measurement of calprotectin medically necessary for the management of inflammatory bowel diseases (e.g., Crohn's disease, ulcerative colitis) and for distinguishing inflammatory bowel diseases from irritable bowel syndrome

Fecal Calprotectin

HERC staff summary: Fecal calprotectin appears to be a useful test for ruling out inflammatory bowel disease and thus avoiding endoscopy in adults and in children. It also appears to have a role in monitoring disease relapse. It is recommended for use in expert guidelines. It appears to be cost effective as a screening tool to rule out IBS and the need for endoscopy.

HERC staff recommendations:

- 1) Recommend HSD add fecal calprotectin (CPT 83993) to the Diagnostic Procedures File
- 2) Remove the fecal calprotectin (CPT 83993) entry on line 660/GN173

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 660

The following Interventions are prioritized on Line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

| | | | |
|-------|---------------------|--|--|
| 83993 | Calprotectin, fecal | | |
|-------|---------------------|--|--|

Fecal Calprotectin in Pediatric Inflammatory Bowel Disease: A Systematic Review

Ioannis D. Kostakis · Kyriaki G. Cholidou ·
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Abstract

Background Inflammatory bowel disease frequently begins during childhood or adolescence. Current tests and procedures for diagnosing and monitoring inflammatory bowel disease are invasive, uncomfortable and costly. Fecal calprotectin is an inflammatory marker tested in several studies including pediatric patients with inflammatory bowel disease.

Methods A search for articles published up to October 2011 was conducted using MEDLINE and EMBASE databases. We included original English-written articles referred to pediatric patients with inflammatory bowel disease and measured fecal calprotectin levels. We extracted data concerning fecal calprotectin levels in patients with inflammatory bowel disease and in the controls groups, sensitivity, specificity, positive and negative likelihood ratio.

Results Thirty-four studies were included. Fecal calprotectin levels of patients with inflammatory bowel disease are much higher than those of healthy controls or patients with functional disorders or other gastrointestinal diseases. The results vary greatly when taking all studies into consideration. Nevertheless, in cases of newly diagnosed and/or active inflammatory bowel disease, the results are more homogeneous, with high sensitivity and positive likelihood ratio, low negative likelihood ratio, but moderate specificity. Moreover, 50 µg/g seems to be the most proper cut-off point for the fecal calprotectin test.

Conclusions The fecal calprotectin test could be used for supporting diagnosis or confirming relapse of inflammatory bowel disease in pediatric patients. A positive result could confirm the suspicion of either inflammatory bowel disease diagnosis or inflammatory bowel disease relapse, due to the high sensitivity of the test, but a negative result should not exclude these conditions, due to its moderate specificity.

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Keywords Calprotectin · Inflammatory bowel disease ·
Ulcerative colitis · Crohn’s disease · Pediatric

Introduction

The manifestations of inflammatory bowel disease (IBD) frequently begin during childhood or adolescence.

Fecal Calprotectin in Predicting Relapse of Inflammatory Bowel Diseases: A Meta-analysis of Prospective Studies

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Background: Fecal calprotectin (FC) is a relatively new marker of intestinal inflammation. Recently, many studies have extended its role in predicting relapse of quiescent inflammatory bowel disease (IBD), but the reported results have been inconsistent. We aimed to perform a meta-analysis of the predictive capacity of FC in IBD relapse.

Methods: We systematically searched the Medline, Web of Science, Cochrane Library, and EMBASE databases for prospective studies that used FC concentrations at remission in predicting relapse of Crohn's disease (CD) and ulcerative colitis (UC). Pooled sensitivity, specificity, and other diagnostic indices were evaluated.

Results: A total of 672 IBD patients (318 UC and 354 CD) from six different studies were analyzed. The pooled sensitivity and specificity of FC to predict relapse of quiescent IBD was 78% (95% confidence interval [CI]: 72–83) and 73% (95% CI: 68–77), respectively. The area under the summary receiver-operating characteristic (sROC) curve was 0.83 and the diagnostic odds ratio was 10.31 (95% CI: 5.05–21.06). The capacity of FC to predict relapse was comparable between UC and CD. In CD patients the predictive value of FC in isolated small bowel CD was not assessed due to insufficiency of available data. Compared with all enrolled CD patients, FC appeared to be more accurate in ileocolonic and colonic CD.

Conclusions: As a simple and noninvasive marker, FC is useful to predict relapse in quiescent IBD patients.

(*Inflamm Bowel Dis* 2012;18:1894–1899)

Key Words: Inflammatory bowel disease, Crohn's disease, ulcerative colitis, fecal calprotectin

The natural clinical course of inflammatory bowel disease (IBD) is characterized by episodes of relapse and remission. The main treatment goal in IBD is to induce and maintain remission by effective suppression of gut inflammation. Despite successful medical treatment, subclinical inflammation may still exist in the bowel, leading to significant risk of relapse.^{1–3} Thus, detection of such inflammation and identifying patients at high risk of relapse are of great clinical significance, as they may have therapeutic implications. Currently, serological biomarkers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are widely used as noninvasive parameters for IBD. However, they have insufficient sensitivity and specificity for intestinal inflammation.^{4–6}

Fecal calprotectin (FC) is an excellent marker of intestinal inflammation, as it reflects the migration of neutrophils through the inflamed bowel wall to the mucosa.⁷ FC appears to have good diagnostic precision in distinguishing IBD from non-IBD patients.⁸ Moreover, FC concentrations correlate well with histological and endoscopic inflammation.^{9,10} Recently, extending the use of FC to predict relapse of ulcerative colitis (UC) and Crohn's disease (CD) patients has attracted significant interest and has been the focus of a growing number of publications.^{11–24} However, the results reported are variable and controversial. The objective of this study was to assess the overall capacity of FC in predicting relapse of IBD with a meta-analysis.

MATERIALS AND METHODS

Literature Search

We searched the electronic databases including MEDLINE (using PubMed as the search engine), EMBASE, Web of Science, and the Cochrane Database were searched to identify suitable studies up to August 2011, without restrictions on language. The MeSH headings and key words used were “calprotectin and Crohn's disease,” “calprotectin and ulcerative colitis,” “calprotectin and IBD,” “Leukocyte L1 complex and IBD,” “calprotectin and feces,” “calprotectin and relapse,”

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Erratum: Ulcerative Colitis Practice Guidelines in Adults: American College of Gastroenterology, Practice Parameters Committee

Asher Kornbluth, David B Sachar and The Practice Parameters Committee of the American College of Gastroenterology

Am J Gastroenterol 2010;105:500; doi:10.1038/ajg.2010.52; published online 23 February 2010

Correction to: *Am J Gastroenterol* 2010;105:501–523; doi:10.1038/ajg.2009.727

In the Conflict of Interest section of the article, the Financial Support subsection should have stated that “No support was provided for this work.” The publisher regrets any confusion this misstatement may have caused.

The corrected Potential Competing Interests subsection for Dr Kornbluth is as follows:

“Asher Kornbluth is a consultant for Salix Pharmaceutical, Shire Pharmaceutical, Procter and Gamble Pharmaceutical, Centocor, and Prometheus Laboratory and has received research support from Salix Pharmaceutical, Procter and Gamble Pharmaceuticals, and Centocor Inc. He is also on the Speaker’s Bureau of Salix Pharmaceutical, Shire Pharmaceutical, Procter and Gamble Pharmaceutical, Centocor, Prometheus, and Axcan Pharmaceutical.”

Also in the Conflict of Interest section, Dr Sachar’s Potential Competing Interests statement was not included. It is as follows:

“David Sachar serves as expert witness for the plaintiffs in litigation claiming that isotretinoin was a cause of their inflammatory bowel disease. He has no other conflicts of interest to report.”

CME

Ulcerative Colitis Practice Guidelines in Adults: American College of Gastroenterology, Practice Parameters Committee

Asher Kornbluth, MD¹, David B. Sachar, MD, MACG¹ and The Practice Parameters Committee of the American College of Gastroenterology

Guidelines for clinical practice are aimed to indicate preferred approaches to medical problems as established by scientifically valid research. Double-blind placebo controlled studies are preferable, but compassionate-use reports and expert review articles are used in a thorough review of the literature conducted through Medline with the National Library of Medicine. When only data that will not withstand objective scrutiny are available, a recommendation is identified as a consensus of experts. Guidelines are applicable to all physicians who address the subject regardless of specialty training or interests and are aimed to indicate the preferable but not necessarily the only acceptable approach to a specific problem. Guidelines are intended to be flexible and must be distinguished from standards of care, which are inflexible and rarely violated. Given the wide range of specifics in any health-care problem, the physician must always choose the course best suited to the individual patient and the variables in existence at the moment of decision. Guidelines are developed under the auspices of the American College of Gastroenterology and its Practice Parameters Committee and approved by the board of trustees. Each has been intensely reviewed and revised by the Committee, other experts in the field, physicians who will use them, and specialists in the science of decision analysis. The recommendations of each guideline are therefore considered valid at the time of composition based on the data available. New developments in medical research and practice pertinent to each guideline will be reviewed at a time established and indicated at publication to assure continued validity. The recommendations made are based on the level of evidence found. Grade A recommendations imply that there is consistent level 1 evidence (randomized controlled trials), grade B indicates that the evidence would be level 2 or 3, which are cohort studies or case-control studies. Grade C recommendations are based on level 4 studies, meaning case series or poor-quality cohort studies, and grade D recommendations are based on level 5 evidence, meaning expert opinion.

Am J Gastroenterol 2010; 105:501–523; doi:10.1038/ajg.2009.727; published online 12 January 2010

INTRODUCTION

Ulcerative colitis (UC) is a chronic disease characterized by diffuse mucosal inflammation limited to the colon. It involves the rectum in about 95% of cases and may extend proximally in a symmetrical, circumferential, and uninterrupted pattern to involve parts or all of the large intestine. The hallmark clinical symptom is bloody diarrhea often with prominent symptoms of rectal urgency and tenesmus. The clinical course is marked by exacerbations and remissions, which may occur spontaneously or in response to treatment changes or intercurrent illnesses (1,2). UC affects approximately 500,000 individuals in the United States with an incidence of 8–12 per 100,000 population per year; the incidence has remained relatively constant over the last five decades (3–8).

The disease accounts for a quarter million physician visits annually, 30,000 hospitalizations, and loss of over a million

workdays per year (9). The direct medical costs alone exceed four billion dollars annually, comprising estimated hospital costs of over US\$960 million (10,11) and drug costs of \$680 million (11).

RECOMMENDATIONS FOR DIAGNOSIS AND ASSESSMENT

In a patient presenting with persistent bloody diarrhea, rectal urgency, or tenesmus, stool examinations and sigmoidoscopy or colonoscopy and biopsy should be performed to confirm the presence of colitis and to exclude the presence of infectious and noninfectious etiologies. Characteristic endoscopic and histologic findings with negative evaluation for infectious causes will suggest the diagnosis of UC.

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The diagnosis of UC is suspected on clinical grounds and supported by the appropriate findings on proctosigmoidoscopy or colonoscopy, biopsy, and by negative stool examination for infectious causes (12). Inquiries should be made regarding factors that may potentially exacerbate symptoms of UC; e.g., smoking cessation or nonsteroidal anti-inflammatory drug use or possibly isotretinoin (13–16). Infections can also produce clinical findings indistinguishable from idiopathic UC, so microbiologic studies for bacterial infection (including specific assays for *Escherichia coli* 0157:H7) and parasitic infestation, as well as serologic testing for ameba when clinical suspicion is high, should be performed in each new patient (17), and should be considered in patients in remission or with mild stable symptoms who unexpectedly develop a severe or atypical exacerbation (18,19). Similarly, patients who have recently been admitted to hospital or treated with antibiotics should have stools examined for *Clostridium difficile*, although antibiotic-associated diarrhea may be present even with a negative assay for *C. difficile* toxin. The incidence of *C. difficile* is increasing in UC (20–23), and in inflammatory bowel disease (IBD) patients it is associated with a more severe course, greater length of hospital stay, higher financial costs, greater likelihood of colectomy, and increased mortality (22,24). Multiple stool assays may be required for diagnosis because of frequent false-negative results (22,24,25).

Proctosigmoidoscopy or colonoscopy will reveal the mucosal changes characteristic of UC, consisting of loss of the typical vascular pattern, granularity, friability, and ulceration (26–28). These changes typically involve the distal rectum, both endoscopically and histologically (29) and proceed proximally in a symmetric, continuous, and circumferential pattern to involve all or part of the colon. However, isolated patchy cecal inflammation is often seen in UC patients with otherwise only distal disease (30). These endoscopic features may not present in a typical manner in UC patients who have already received treatment, in which case-selective healing may have resulted in skip areas and rectal sparing. Because none of these endoscopic findings is specific for UC, histologic findings obtained from biopsies may be helpful in the differential diagnosis (31). Imaging of the small bowel may also be helpful when the diagnosis of Crohn's disease (CD) is being considered (32,33).

In the patient with acute onset of bloody diarrhea, the mucosal biopsy may help distinguish UC from infectious colitis. In UC, more commonly than in infectious colitis, the mucosa shows separation, distortion, and atrophy of crypts; chronic inflammatory cells in the lamina propria; preferential homing of neutrophils to the crypt epithelium; increased number of lymphocytes and plasma cells at the crypt bases; "shortfall" of crypts not reaching to the muscularis mucosae; and basal lymphoid aggregates (12,34–36). Villous mucosal architecture and Paneth cell metaplasia on rectal biopsy are other features favoring the diagnosis of UC (37). Crypt abscesses, on the other hand, are a nonspecific indication of inflammation and do not indicate a particular diagnosis (38). However, a large, bulging, cystic dilation with a small "necklace" of flat or cuboidal

cells around the crypt abscess is more common in infectious, or acute self-limited colitis, than it is in UC (12). CD may be suggested by certain histologic findings such as noncaseating granulomas or microscopic focality, but their absence does not rule out the diagnosis. Furthermore, even in UC or in acute self-limited colitis, muciphage (or "cryptolytic") granulomas may form in response to ruptured crypts and are therefore not pathognomonic for CD (37). "Backwash ileitis" may occur in UC and appears as mild ileal inflammation endoscopically; it is almost always associated with cecal inflammation and has characteristic histologic findings of mild villous atrophy and only scattered crypt abscesses (39).

Other histologic findings that may suggest an infectious etiology include caseating or confluent granulomas in tuberculosis (TB) (or less commonly in schistosomiasis, syphilis, and *Chlamydia trachomatis*), trophozoites in amebiasis, pseudomembranes in *C. difficile* colitis (although in UC, most cases of *C. difficile* infection occur in the absence of pseudomembranes) (22), ova in schistosomiasis, and viral inclusions in herpetic or cytomegaloviral colitis, although the latter appears almost exclusively in immunocompromised patients (see "Recommendations for management of severe colitis"). In the appropriate clinical settings, sigmoidoscopy or colonoscopy and biopsy may also distinguish the various noninfectious colitides from UC. These conditions include ischemia, radiation, collagenous and microscopic colitis, drug-induced colitis, and the solitary rectal ulcer syndrome (38,40,41). Segmental colitis associated with diverticulosis, which usually presents with painless hematochezia in patients older than 60, is distinguished from UC by its segmental location in an area of diverticula, typically in the sigmoid colon and with rectal sparing (42–44).

Perinuclear antineutrophil cytoplasmic antibodies (pANCA) have been identified in 60–70% of UC patients, but are also found in up to 40% of patients with CD. These pANCA-positive CD patients typically have a clinical phenotype resembling left-sided UC, so pANCA detection alone is of little value in distinguishing between UC and Crohn's colitis (45). However, reactivity to CBir 1, an anti-flagellin antibody, is preferentially present in pANCA-positive CD patients as compared with pANCA-positive UC patients, 44% vs. 4%, respectively (46). A meta-analysis of 60 studies analyzing performance characteristics of pANCA and anti-saccharomyces cerevisiae antibodies in 3,841 UC patients and 4,019 CD patients found a specificity of 89% pANCA for UC, but a sensitivity of only 59%. For patients with CD, a positive anti-saccharomyces cerevisiae antibodies with a negative ANCA had a specificity of 93% for CD, but again with a sensitivity of only 55% (47). The low sensitivity of pANCA for the diagnosis of UC prevents it from serving as a useful diagnostic tool. However, their specificities may make these assays useful in the occasional patient in whom no other clinical or pathologic features allow a differential diagnosis between UC and Crohn's colitis (48,49). Although this distinction is not always crucial, it may have important consequences in terms of counseling, prognosis, and the choice of medical and surgical therapies (50).

Pulmonary Rehabilitation

Question: Should a guideline limiting pulmonary rehabilitation be added to the Prioritized List?

Question source: Tuality Healthcare CCO

Issue: Pulmonary rehabilitation is on multiple lines on the Prioritized List with no limitations on coverage. Pulmonary rehabilitation is a broad program that helps improve the well-being of people who have chronic respiratory conditions such as COPD (chronic obstructive pulmonary disease), sarcoidosis, idiopathic pulmonary fibrosis, or cystic fibrosis. Pulmonary rehabilitation is a multi-disciplinary treatment that might include exercise training, nutritional counseling, education, breathing strategies, psychological counseling, etc. Pulmonary rehabilitation is normally an outpatient therapy, but may be provided in a patient's home.

From Tuality Healthcare:

I wanted to inquire if we could possibly get a Pulmonary Rehab guideline note designed? Currently there is no such thing, although Medicare covers Pulmonary Rehab when it is "moderate to very severe" which has many different definitions according to different resources, so we're a bit unsure if we should be using the FEV, the mMRC or the CAT scores to determine this ranking. Also currently Medicare covers up to 36 sessions over the patient's lifetime, so should we be using the same guidelines? Any coverage guidance within this subject would be incredibly helpful.

Current Prioritized List status:

G0237 (Therapeutic procedures to increase strength or endurance of respiratory muscles, face to face, one on one, each 15 minutes (includes monitoring)), G0238 (Therapeutic procedures to improve respiratory function, other than described by G0237, one on one, face to face, per 15 minutes (includes monitoring)), G0239 (Therapeutic procedures to improve respiratory function or increase strength or endurance of respiratory muscles, two or more individuals (includes monitoring)), and S9437 (Pulmonary rehabilitation program, non-physician provider, per diem) are on the Ancillary Procedures File.

G0424 (Pulmonary rehabilitation, including exercise (includes monitoring), one hour, per session, up to two sessions per day) is on lines 9 ASTHMA, 58 BRONCHIECTASIS, 223 OCCUPATIONAL LUNG DISEASES, 234 ADULT RESPIRATORY DISTRESS SYNDROME; ACUTE RESPIRATORY FAILURE; RESPIRATORY CONDITIONS DUE TO PHYSICAL AND CHEMICAL AGENTS, 241 CONDITIONS REQUIRING HEART-LUNG AND LUNG TRANSPLANTATION, 283 CHRONIC OBSTRUCTIVE PULMONARY DISEASE; CHRONIC RESPIRATORY FAILURE.

Pulmonary Rehabilitation

Evidence

- 1) **Puhan 2016**, Cochrane review of pulmonary rehabilitation for COPD
<https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005305.pub4/epdf/full>
 - a. N=20 studies (1477 patients)
 - b. Eight studies involving 810 participants contributed data on hospital readmissions. Moderate-quality evidence indicates that pulmonary rehabilitation reduced hospital readmissions (pooled odds ratio (OR) 0.44, 95%confidence interval (CI) 0.21 to 0.91), but results were heterogenous (I² = 77%).
 - c. Six studies including 670 participants contributed data on mortality. The quality of evidence was low, and the meta-analysis did not show a statistically significant effect of rehabilitation on mortality (pooled OR 0.68, 95% CI 0.28 to 1.67). Again, results were heterogenous (I² = 59%).
 - d. Hospital readmissions and mortality studies newly included in this update showed, on average, significantly smaller effects of rehabilitation than were seen in earlier studies.
 - e. High-quality evidence suggests that pulmonary rehabilitation after an exacerbation improves health-related quality of life.
 - f. Five studies involving 278 participants explicitly recorded adverse events, four studies reported no adverse events during rehabilitation programmes and one study reported one serious event.
 - g. **Authors' conclusions** Overall, evidence of high quality shows moderate to large effects of rehabilitation on health-related quality of life and exercise capacity in patients with COPD after an exacerbation. Some recent studies showed no benefit of rehabilitation on hospital readmissions and mortality and introduced heterogeneity as compared with the last update of this review. Such heterogeneity of effects on hospital readmissions and mortality may be explained to some extent by the extensiveness of rehabilitation programmes and by the methodological quality of the included studies.
- 2) **Dowman 2014**, Cochrane review of pulmonary rehabilitation for interstitial lung disease
<https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006322.pub3/epdf/full>
 - a. N=9 studies
 - b. No adverse effects of pulmonary rehabilitation were reported.
 - c. Pulmonary rehabilitation improved the six-minute walk distance with weighted mean difference (WMD) of 44.34 meters (95% confidence interval (CI) 26.04 to 62.64 meters) vs -0.4 to 17 meters for control patients [note: clinically meaningful improvement for this test is defined as a >30 meter gain] and improved oxygen consumption (VO₂) peak with WMD of 1.24 mL/kg/min (95% CI 0.46 to 2.03 mL/kg/min) vs -0.02 to 0.4 ml/kg/min for controls.
 - d. Quality of life improved following pulmonary rehabilitation for all participants on a variety of measures (SMD 0.59, 95% CI 0.20 to 0.98)
 - e. Two studies reported longer-term outcomes, with no significant effects of pulmonary rehabilitation on clinical variables or survival at three or six months.
 - f. **Authors' conclusions:** Pulmonary rehabilitation seems to be safe for people with ILD. Improvements in functional exercise capacity, dyspnoea and quality of life are seen immediately following pulmonary rehabilitation. Because of inadequate reporting of methods and small numbers of included participants, the quality of evidence was low to moderate. Little evidence was available regarding longer-term effects of pulmonary rehabilitation.

Pulmonary Rehabilitation

Expert guidelines

- 1) **ACCP/AACVPR 2007**, evidence based guideline on pulmonary rehabilitation [https://journal.chestnet.org/article/S0012-3692\(16\)30215-X/pdf](https://journal.chestnet.org/article/S0012-3692(16)30215-X/pdf)
 - a. A program of exercise training of the muscles of ambulation is recommended as a mandatory component of pulmonary rehabilitation for patients with COPD. Grade of recommendation, 1A
 - b. Pulmonary rehabilitation improves the symptom of dyspnea in patients with COPD: Grade of recommendation, 1A
 - c. Pulmonary rehabilitation improves health related quality of life in patients with COPD. Grade of recommendation, 1A
 - d. Pulmonary rehabilitation reduces the number of hospital days and other measures of health-care utilization in patients with COPD. Grade of recommendation, 2B
 - e. Pulmonary rehabilitation is cost-effective in patients with COPD. Grade of recommendation, 2C
 - f. There is insufficient evidence to determine whether pulmonary rehabilitation improves survival in patients with COPD. No recommendation is provided.
 - g. There are psychosocial benefits from comprehensive pulmonary rehabilitation programs in patients with COPD. Grade of recommendation, 2B
 - h. Six to twelve weeks of pulmonary rehabilitation produces benefits in several outcomes that decline gradually over 12 to 18 months. Grade of recommendation, 1A. Some benefits, such as HRQOL, remain above control levels at 12 to 18 months. Grade of recommendation, 1C
 - i. Longer pulmonary rehabilitation programs (beyond 12 weeks) produce greater sustained benefits than shorter programs. Grade of recommendation, 2C
 - j. Maintenance strategies following pulmonary rehabilitation have a modest effect on long-term outcomes. Grade of recommendation, 2C
 - k. Education should be an integral component of pulmonary rehabilitation. Education should include information on collaborative self-management, and the prevention and treatment of exacerbations. Grade of recommendation, 1B
 - l. Pulmonary rehabilitation is beneficial for patients with some chronic respiratory diseases other than COPD. Grade of recommendation, 1B
- 2) **British Thoracic Society 2013**, guideline on pulmonary rehabilitation in adults <https://www.brit-thoracic.org.uk/document-library/clinical-information/pulmonary-rehabilitation/bts-guideline-for-pulmonary-rehabilitation/>
 - a. As a minimum, efficacy of pulmonary rehabilitation programmes needs to be regularly assessed by demonstrating clinically important improvements in exercise capacity, dyspnoea and health status. (Grade B)
 - b. Patients with a Medical Research Council (MRC) Dyspnoea score of 3–5 who are functionally limited by breathlessness should be referred for outpatient pulmonary rehabilitation. (Grade A)
 - c. Patients with a MRC dyspnoea score of 2 who are functionally limited by breathlessness should be referred for pulmonary rehabilitation. (Grade D)
 - d. Patients with a MRC dyspnoea score of 5 who are housebound should not routinely be offered supervised pulmonary rehabilitation within their home. (Grade B)

Pulmonary Rehabilitation

- e. Patients with unstable cardiac disease or locomotor difficulties that preclude exercise (eg, severe arthritis or severe peripheral vascular disease) should not be referred for pulmonary rehabilitation.
 - f. Pulmonary rehabilitation programmes should be a minimum of twice-weekly supervised sessions. (Grade D)
 - g. Pulmonary rehabilitation programmes of 6–12 weeks are recommended. (Grade A)
 - h. Pulmonary rehabilitation programmes including the attendance at a minimum of 12 supervised sessions are recommended, although individual patients can gain some benefit from fewer sessions. (Grade A)
 - i. Repeat pulmonary rehabilitation should be considered in patients who have completed a course of pulmonary rehabilitation more than 1 year previously. The likely benefits should be discussed and willing patients referred. (Grade B)
 - j. Earlier repeat pulmonary rehabilitation should be considered in individuals with accelerated physiological decline or if additional benefits on a shorter timescale would be clinically valuable. (Grade D)
 - k. It is unlikely that if the patient completed the pulmonary rehabilitation course originally and failed to gain a benefit, they would benefit a second time round, unless circumstances such as an exacerbation interrupted the initial programme.
- 3) **Canadian Thoracic Society 2010**, guideline on pulmonary rehabilitation
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2933771/pdf/crj17159.pdf>
- a. Length of rehabilitation program:
 - i. based on limited evidence from six studies and consensus of the expert panel
 - ii. it is recommended that longer PR programs, beyond six to eight weeks duration, be provided for COPD patients. (GRADE: 2B)
 - b. Which patients benefit from pulmonary rehabilitation?
 - i. based on evidence from five studies and consensus of the expert panel.
 - ii. Evidence supports PR for patients with moderate, severe and very severe COPD (GRADE: 1C)
 - iii. There are insufficient data to make a recommendation regarding patients with mild COPD
 - iv. It is uncertain whether prescribing PR to all patients regardless of disease severity is cost effective
 - c. Should patients start PR within one month of an acute exacerbation of COPD?
 - i. It is strongly recommended that COPD patients undergo pulmonary rehabilitation within one month following an AECOPD due to evidence supporting improved dyspnea, exercise tolerance and health related quality of life compared with usual care (GRADE 1B)
 - ii. Pulmonary rehabilitation within one month following an AECOPD is also recommended due to evidence supporting reduced hospital admissions and mortality compared with usual care (GRADE 2C)

Other coverage policies

- 1) **CMS 2010**, NCD for pulmonary rehabilitation
 - a. Pulmonary rehabilitation is covered if it is a physician-supervised, comprehensive PR program for patients with moderate to very severe COPD. Medicare will pay for up to two (2) one-hour sessions per day, for up to 36 lifetime sessions (in some cases, up to 72

Pulmonary Rehabilitation

lifetime sessions) of PR. The PR program must include the following mandatory components:

- i. Physician-prescribed exercise;
 - ii. Education or training;
 - iii. Psychosocial assessment;
 - iv. Outcomes assessment; and
 - v. An individualized treatment plan.
- 2) **NICE 2016**, management of COPD <https://www.nice.org.uk/guidance/qs10/resources/chronic-obstructive-pulmonary-disease-in-adults-pdf-2098478592709>
- a. People with stable COPD and exercise limitation due to breathlessness are referred to a pulmonary rehabilitation programme.
 - i. Rationale: Pulmonary rehabilitation programmes improve a person's exercise capacity, quality of life, symptoms and levels of anxiety and depression
 - b. People admitted to hospital for an acute exacerbation of COPD start a pulmonary rehabilitation programme within 4 weeks of discharge.
 - c. Programmes comprise individualised exercise programmes and education, and:
 - i. are at least 6 weeks in duration and include a minimum of twice-weekly supervised sessions
 - ii. include supervised, individually tailored and prescribed, progressive exercise training including both aerobic and resistance training
 - iii. include a defined, structured education programme.
 - d. Pulmonary rehabilitation is not suitable for people with unstable cardiac disease, locomotor or neurological difficulties precluding exercise such as severe arthritis or peripheral vascular disease, and people in a terminal phase of an illness or with significant cognitive or psychiatric impairment.
- 3) **Aetna 2018**
- a. Aetna considers entry into a medically supervised outpatient pulmonary rehabilitation program medically necessary when *all* of the following criteria are met:
 - i. Member has chronic pulmonary disease (including alpha-1 antitrypsin deficiency, asbestosis, asthma, emphysema, chronic airflow obstruction, chronic bronchitis, cystic fibrosis, fibrosing alveolitis, pneumoconiosis, pulmonary alveolar proteinosis, pulmonary fibrosis, pulmonary hemosiderosis, radiation pneumonitis), or other conditions that affect pulmonary function such as ankylosing spondylitis, bronchopulmonary dysplasia, Guillain-Barre' syndrome or other infective polyneuritis, muscular dystrophy, myasthenia gravis, paralysis of diaphragm, sarcoidosis, or scoliosis; *and*
 - ii. Member has dyspnea at rest or with exertion; *and*
 - iii. Member has a reduction in exercise tolerance that restricts the ability to perform activities of daily living and/or work; *and*
 - iv. Symptoms persist despite appropriate medical management; *and*
 - v. Member does not have a recent history of smoking or has quit smoking for at least 3 months; *and*
 - vi. Member has a moderate to severe functional pulmonary disability as evidenced by *either* of the following:
 1. A maximal pulmonary exercise stress test under optimal bronchodilatory treatment which demonstrates a respiratory limitation to exercise with a maximal oxygen uptake (VO₂max) equal to or less than 20 ml/kg/min, or about 5 metabolic equivalents (METS); *or*

Pulmonary Rehabilitation

2. Pulmonary function tests showing that either the forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC ratio, or diffusion capacity for carbon monoxide (Dlco) is less than 60 % of that predicted; *and*
 - vii.* Member is physically able, motivated and willing to participate in the pulmonary rehabilitation program and be a candidate for self-care post program; *and*
 - viii.* Member does not have *any* concomitant medical condition that would otherwise imminently contribute to deterioration of pulmonary status or undermine the expected benefits of the program (e.g., symptomatic coronary artery disease, congestive heart failure, myocardial infarction within the last 6 months, dysrhythmia, active joint disease, claudication, malignancy).
- b.* Aetna considers pulmonary rehabilitation medically necessary for persons receiving a medically necessary lung transplantation
- c.* Aetna considers repeat pulmonary rehabilitation programs not medically necessary. However, exceptions may be made for patients undergoing a repeat pulmonary rehabilitation program in connection with lung transplantation or lung volume reduction surgery.
- d.* Aetna considers pre-operative pulmonary rehabilitation in persons undergoing surgery for lung cancer experimental and investigational because the effectiveness of this approach has not been established.
- e.* Pulmonary rehabilitation is *not* considered medically necessary in persons who have very severe pulmonary impairment as evidenced by dyspnea at rest, difficulty in conversation (one-word answers), inability to work, cessation of most of all usual activities making them housebound and often limiting them to bed or chair with dependency upon assistance from others for most ADL. According to available guidelines, persons with very severe pulmonary impairment are not appropriate candidates for pulmonary rehabilitation.
- f.* A typical course of pulmonary rehabilitation extends for up to 6 weeks or 36 hours of therapy.
- g.* Coverage of pulmonary rehabilitation may be subject to applicable limits on short-term rehabilitation.

CCO feedback to proposed guideline:

- 1) The only comment received was that some CCOs do not PA pulmonary rehabilitation because it is underutilized. The guideline was felt be appropriate.

Pulmonary Rehabilitation

HERC staff summary

Pulmonary rehabilitation programs have evidence of benefit for increased quality of life and increased exercise ability in patients with a variety of chronic respiratory illnesses. There is mixed or insufficient evidence of effectiveness for decreasing hospitalizations and improving mortality.

Most expert guideline and other payer policies recommend pulmonary rehabilitation for moderate or severe respiratory disease for patients without severe comorbid conditions or who are not housebound. Pulmonary rehabilitation must be a multidisciplinary program including exercise and education. Most recommendations are for a minimum of 2 sessions per week for 6-12 weeks. US policies generally limit pulmonary rehabilitation to 36 hours. Repeat pulmonary rehabilitation programs should be limited to those patients who successfully completed a previous program more than one year prior, particularly if that patient has lung surgery; although there is no evidence of benefit of repeat programs.

HERC staff recommendations

- 1) Add pulmonary rehabilitation HCPCS codes to lines with chronic pulmonary disease diagnoses
 - a. HCPCS codes:
 - i. G0237 (Therapeutic procedures to increase strength or endurance of respiratory muscles, face to face, one on one, each 15 minutes (includes monitoring))
 - ii. G0238 (Therapeutic procedures to improve respiratory function, other than described by G0237, one on one, face to face, per 15 minutes (includes monitoring))
 - iii. G0239 (Therapeutic procedures to improve respiratory function or increase strength or endurance of respiratory muscles, two or more individuals (includes monitoring))
 - iv. S9437 (Pulmonary rehabilitation program, non-physician provider, per diem) are on the Ancillary Procedures File.
 - v. Note: G0424 is already on the lines below
 - b. Lines:
 - i. 9 ASTHMA
 - ii. 58 BRONCHIECTASIS
 - iii. 223 OCCUPATIONAL LUNG DISEASES
 - iv. 234 ADULT RESPIRATORY DISTRESS SYNDROME; ACUTE RESPIRATORY FAILURE; RESPIRATORY CONDITIONS DUE TO PHYSICAL AND CHEMICAL AGENTS
 - v. 241 CONDITIONS REQUIRING HEART-LUNG AND LUNG TRANSPLANTATION
 - vi. 283 CHRONIC OBSTRUCTIVE PULMONARY DISEASE; CHRONIC RESPIRATORY FAILURE.
- 2) Add a new guideline for pulmonary rehabilitation as shown below

GUIDELINE NOTE XXX, PULMONARY REHABILITATION

Lines 9,58,234,241,283

Pulmonary rehabilitation is included on these lines only for patients with all of the following:

- 1) moderate to severe chronic pulmonary disease with dyspnea with exertion that reduces their ability to perform activities of daily living despite appropriate medical management, *and*
- 2) moderate to severe pulmonary disability defined as either
 - a. A maximal pulmonary exercise stress test under optimal bronchodilatory treatment which demonstrates a respiratory limitation to exercise with a maximal oxygen

Pulmonary Rehabilitation

uptake (VO₂max) equal to or less than 20 ml/kg/min, or about 5 metabolic equivalents (METS); *or*

- b. Pulmonary function tests showing that either the forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), FEV₁/FVC ratio, or diffusion capacity for carbon monoxide (Dlco) is less than 60 % of that predicted; *and*
- 3) physically able, motivated and willing to participate in the pulmonary rehabilitation program and be a candidate for self-care post program; *and*
- 4) no contraindications to pulmonary rehabilitation, including unstable cardiac disease, locomotor or neurological difficulties precluding exercise, significant cognitive or psychiatric impairment, or housebound due to the severity of disease.

Pulmonary rehabilitation is only covered for

- 1) A multidisciplinary program with includes supervised exercise therapy, patient education, and smoking cessation (if applicable).
- 2) A minimum of 2 session per week for 6-12 weeks.

Repeat pulmonary rehabilitation programs should be limited to those patients who successfully completed a previous program more than one year prior and who have had a significant change in their health status.

Portions of the pulmonary rehabilitation program that include services in GUIDELINE NOTE 6, REHABILITATIVE AND HABILITATIVE THERAPIES are included in the visit totals in that guideline.



News Flash – As a result of the Affordable Care Act (ACA), claims with dates of service on or after January 1, 2010, received later than one calendar year beyond the date of service will be denied by Medicare. For full details, see the MLN Matters® article, MM6960, at <http://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/downloads/MM6960.pdf> on the Centers for Medicare & Medicaid Services website.

MLN Matters® Number: MM6823 **Revised**

Related Change Request (CR) #: 6823

Related CR Release Date: May 7, 2010

Effective Date: January 1, 2010

Related CR Transmittal #: R124BP and R1966CP

Implementation Date: October 4, 2010

Pulmonary Rehabilitation (PR) Services

Note: This article was updated on November 23, 2012, to reflect current Web addresses. This article was previously revised on July 16, 2012, to add clarifying language, as contained in CR6823, to show that the covered benefit for the comprehensive PR program is for patients with moderate to very severe COPD. All other information is the same.

Provider Types Affected

This article is for physicians and providers submitting claims to Medicare contractors (Medicare Administrative Contractors (A/B MACs), Fiscal Intermediaries (FIs) and/or carriers) for pulmonary rehabilitation (PR) services provided to Medicare beneficiaries.

Provider Action Needed

This article is based on Change Request (CR) 6823 which alerts providers that the Medicare Improvements for Patients and Providers Act (MIPPA) of 2008 added payment and coverage improvements for patients with chronic obstructive pulmonary disease (COPD) and other conditions effective January 1, 2010. As a result, Medicare provides a covered benefit for a comprehensive PR program for patients with moderate to very severe COPD under Medicare Part B effective for services on or after January 1, 2010. Be certain your billing staffs are aware of these Medicare changes and of the claims processing system changes to handle

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claims for PR services that must be implemented no later than October 4, 2010.

Background

Pulmonary Rehabilitation (PR) is a multi-disciplinary program of care for patients with chronic respiratory impairment who are symptomatic and often have decreased daily life activities.

.A PR program is individually tailored and designed to optimize physical and social performance and autonomy. The program must provide an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory impairment. In September 2007, the Centers for Medicare & Medicaid Services (CMS), in its final decision memorandum for PR Services, announced there was no basis for a national coverage determination at that time. Specifically, this decision was based on a determination by CMS that the Social Security Act did not expressly define a comprehensive PR program as a Part B benefit, and the evidence was not adequate to draw conclusions on the benefit of the individual components of PR. CMS did (and still does) cover medically reasonable and necessary respiratory treatment services in Comprehensive Outpatient Rehabilitation Facilities (CORFs), as well services to patients with respiratory impairments who are not eligible for PR but for whom local contractors determine respiratory treatment services are covered. MIPPA added payment and coverage improvements for patients with COPD and other conditions, and now provides a covered benefit for a comprehensive PR program for patients with moderate to very severe COPD under Medicare Part B effective January 1, 2010. This law authorizes a PR program, which was codified in the Physician Fee Schedule calendar year 2010 final rule at 42 CFR 410.47.

Key Points of CR 6823

Effective January 1, 2010, MIPPA provisions added a physician-supervised, comprehensive PR program for patients with moderate to very severe COPD. Medicare will pay for up to two (2) one-hour sessions per day, for up to 36 lifetime sessions (in some cases, up to 72 lifetime sessions) of PR. The PR program must include the following mandatory components:

1. Physician-prescribed exercise;
2. Education or training;
3. Psychosocial assessment;
4. Outcomes assessment; and
5. An individualized treatment plan.

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The following bullet points detail Medicare claims processing requirements for PR services furnished on or after January 1, 2010:

- Effective January 1, 2010, Medicare contractors will pay claims containing Healthcare Common procedure Coding System (HCPCS) code G0424 when billing for PR services, including exercise and monitoring, as described in the Medicare Benefit Policy Manual, Chapter 15, section 231, as revised by CR 6823, and the Medicare Claims Processing Manual, Chapter 32, Section 140, as revised by CR 6823. These revised documents are attached to CR 6823, which is available at <http://www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/downloads/R124BP.pdf> (Benefit Policy Manual) and <http://www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/downloads/R1966CP.pdf> (Claims Processing Manual) on the CMS website.
- Medicare contractors will pay claims for HCPCS code G0424 (PR) only when services are provided in the following places of service (POS): 11 (physician's office) or 22 (hospital outpatient). Medicare will deny claims for HCPCS code G0424 performed in other than, and billed without, POS 11 or 22, using the following:
 - Claim Adjustment Reason Code (CARC) 58 – “treatment was deemed by the payer to have been rendered in an inappropriate or invalid place of service. NOTE: Refer to the 835 Healthcare Policy Identification Segment (loop 2110 Service Payment Information REF), if present.”
 - Remittance Advice Remark Code (RARC) N428 – “Service/procedure not covered when performed in this place of service.”
 - Group Code PR (Patient Responsibility) assigning financial liability to the patient if the claim was received with a GA modifier indicating a signed Advance Beneficiary Notice (ABN) is on file or Group Code CO (Contractual Obligation) assigning financial liability to the provider if the claim is received with the GZ modifier indicating no signed ABN on file.
- Medicare contractors will pay claims for PR services containing HCPCS code G0424 and revenue code 0948 on Types of Bill (TOB) 13X and 85X under reasonable cost.
- Contractors will pay for PR services for hospitals in Maryland under the jurisdiction of the Health Services Cost Review Commission on an outpatient basis, TOB 13X, in accordance with the terms of the Maryland waiver.

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- Contractors will deny claims for PR services provided in other than TOB 13X and 85X using the following:
 - CARC 58 – “Treatment was deemed by the payer to have been rendered in an inappropriate or invalid place of service. NOTE: Refer to the 835 Healthcare Policy Identification Segment (loop 2110 Service Payment Information REF), if present.”
 - RARC N428 – “Service/procedure not covered when performed in this place of service.”
 - Group Code PR assigning financial liability to the patient if the claim was received with a GA modifier indicating a signed ABN is on file or Group Code CO assigning financial liability to the provider if the claim is received with the GZ modifier indicating no signed ABN on file.
- Using the Medicare Physician Fee Schedule, Medicare contractors will also pay for PR services billed with HCPCS code G0424 and revenue code 096X, 097X, or 098X on TOB 85X from Method II critical access hospitals (CAHs).
- Medicare will deny PR services that exceed two units on the same date of service and, in doing so, will use the following:
 - CARC 119 – “Benefit maximum for this time period or occurrence has been reached.”
 - RARC N362 – “The number of days or units of service exceeds our acceptable maximum.”
 - Group Code PR assigning financial liability to the patient if the claim was received with a GA modifier indicating a signed ABN is on file or Group Code CO assigning financial liability to the provider if the claim is received with the GZ modifier indicating no signed ABN on file.
- Medicare will normally pay for 36 sessions of PR, but may pay up to 72 sessions when the claim(s) for sessions 37-72 includes a KX modifier. Claims for HCPCS code G0424 which exceed 36 sessions without the KX modifier will be denied using the following:
 - CARC 151 – “Payment adjusted because the payer deems the information submitted does not support this many/frequency of services.”
 - Group Code PR assigning financial liability to the patient if the claim was received with a GA modifier indicating a signed ABN is on file or Group Code CO assigning financial liability to the provider if the claim is received with the GZ modifier indicating no signed ABN on file.

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- Medicare contractors will deny claims for HCPCS code G0424 when submitted for more than 72 sessions even where the KX modifier is present. In the denials, contractors will use the following:
 - CARC B5 - "Coverage/program guidelines were not met or were exceeded."
 - Group Code PR assigning financial liability to the patient if the claim was received with a GA modifier indicating a signed ABN is on file or Group Code CO assigning financial liability to the provider if the claim is received with the GZ modifier indicating no signed ABN on file.

Additional Information

If you have questions, please contact your Medicare MAC, FI, or carrier at their toll-free number which may be found at <http://www.cms.gov/Research-Statistics-Data-and-Systems/Monitoring-Programs/provider-compliance-interactive-map/index.html> on the CMS website.

CR6823 was issued to your Medicare MAC, FI, or carrier in two transmittals. One transmittal modifies the Medicare Benefit Policy Manual and that transmittal is available at <http://www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/downloads/R124BP.pdf> on the CMS website. The second transmittal modifies the Medicare Claims Processing Manual and that transmittal is at <http://www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/downloads/R1966CP.pdf> on the CMS website.

For related detailed policy and claims processing instructions issued December 11, 2009, you may review MM6751 at <http://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/downloads/MM6751.pdf> on the CMS website.

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Pulmonary Rehabilitation

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Policy

- I. Aetna considers entry into a medically supervised outpatient pulmonary rehabilitation program medically necessary when *all* of the following criteria are met:
 - A. Member has chronic pulmonary disease (including alpha-1 antitrypsin deficiency, asbestosis, asthma, emphysema, chronic airflow obstruction, chronic bronchitis, cystic fibrosis, fibrosing alveolitis, pneumoconiosis, pulmonary alveolar proteinosis, pulmonary fibrosis, pulmonary hemosiderosis, radiation pneumonitis), or other conditions that affect pulmonary function such as ankylosing spondylitis, bronchopulmonary dysplasia, Guillain-Barre' syndrome or other infective polyneuritis, muscular dystrophy, myasthenia gravis, paralysis of diaphragm, sarcoidosis, or scoliosis; *and*
 - B. Member has dyspnea at rest or with exertion; *and*
 - C. Member has a reduction in exercise tolerance that restricts the ability to perform activities of daily living and/or work; *and*
 - D. Symptoms persist despite appropriate medical management; *and*
 - E. Member does not have a recent history of smoking or has quit smoking for at least 3 months; *and*
 - F. Member has a moderate to severe functional pulmonary disability as evidenced by *either* of the following:
 - A maximal pulmonary exercise stress test under optimal bronchodilatory treatment which demonstrates a respiratory limitation to exercise with a maximal oxygen uptake (VO₂max) equal to or less than 20 ml/kg/min, or about 5 metabolic equivalents (METS); *or*
 - Pulmonary function tests showing that either the forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), FEV₁/FVC ratio, or diffusion capacity for carbon monoxide (Dlco) is less than 60 % of that predicted; *and*
 - G. Member is physically able, motivated and willing to participate in the pulmonary rehabilitation program and be a candidate for self-care post program; *and*
 - H. Member does not have *any* concomitant medical condition that would otherwise imminently contribute to deterioration of pulmonary status or undermine the expected benefits of the program (e.g., symptomatic coronary artery disease, congestive heart failure, myocardial infarction within the last 6 months, dysrhythmia, active joint disease, claudication, malignancy).
- II. Aetna considers pulmonary rehabilitation medically necessary for persons receiving a medically necessary lung transplantation
 - I. [CPB 0597 - Heart-Lung Transplantation](#),
 - II. and [CPB 0598 - Lung Transplantation](#)).

- III. Aetna considers repeat pulmonary rehabilitation programs not medically necessary. However, exceptions may be made for patients undergoing a repeat pulmonary rehabilitation program in connection with lung transplantation or lung volume reduction surgery.
- IV. Aetna considers routine, non-skilled, or maintenance care not medically necessary, such as:
- A. Repetitive services for chronic baseline conditions; *or*
 - B. When there is an inability to sustain gains; *or*
 - C. When there is a plateau in patient's progress toward goals, such that there is minimal or no potential for further substantial progress; *or*
 - D. When there is no overall improvement.
- V. Aetna considers pulmonary rehabilitation experimental and investigational for all other indications because its effectiveness for indications other than the ones listed above has not been established.
- VI. Aetna considers pre-operative pulmonary rehabilitation in persons undergoing surgery for lung cancer experimental and investigational because the effectiveness of this approach has not been established.

Pulmonary rehabilitation is *not* considered medically necessary in persons who have very severe pulmonary impairment as evidenced by dyspnea at rest, difficulty in conversation (one-word answers), inability to work, cessation of most of all usual activities making them housebound and often limiting them to bed or chair with dependency upon assistance from others for most ADL. According to available guidelines, persons with very severe pulmonary impairment are not appropriate candidates for pulmonary rehabilitation.

Note:

- A typical course of pulmonary rehabilitation extends for up to 6 weeks or 36 hours of therapy.
- Coverage of pulmonary rehabilitation may be subject to applicable limits on short-term rehabilitation therapies. Please check benefit plan descriptions for details.
- For lung transplant candidates, pulmonary rehabilitation typically begins when the member is listed for transplant, and continues for 6 weeks after transplantation, at which time the member is transitioned to a home exercise program.
- Most Aetna plans exclude coverage of exercise equipment. Please check benefit plan descriptions for details. Itemized charges for the use, rental, or purchase of exercise equipment may not be covered expenses under these plans. This would include any charges for fitness center or health club memberships.

Background

Comprehensive pulmonary rehabilitation is an outpatient multi-disciplinary program directed to individuals with chronic pulmonary conditions and their families, usually by an inter-disciplinary team of specialists, in an effort to stabilize or reverse both the pathophysiology and psychopathology of their chronic pulmonary disease, with the goal of achieving and maintaining the individual's maximum level of functional capacity and independence in the community allowed by the patient's pulmonary handicap and overall life situation. Examples of conditions that may benefit from pulmonary rehabilitation include, but are not limited to, asthma, bronchiectasis, chronic obstructive pulmonary disease (COPD), cystic fibrosis, pre- or postoperative lung transplant or lung volume surgery or pulmonary fibrosis (interstitial lung disease).

The goal of pulmonary rehabilitation services is not to achieve maximum exercise tolerance, but rather a level of function that allows for the transfer of treatment from the clinic, hospital, or doctor to self-care in the home by the patient, the patient's family, or the patient's caregiver. Unless the patient will be able to conduct ongoing self-care at home, there will be only temporary benefit from the pulmonary rehabilitation services. The endpoint of treatment, therefore, is not when the patient achieves maximal exercise tolerance or stabilizes, but when the patient or his or her attendant is able to continue pulmonary rehabilitation at home. To achieve sustained results, it is important that the

patient continue with an at-home pulmonary rehabilitation regimen.

Primary objectives of pulmonary rehabilitation include: help to restore the ability to function at the highest level of independence in regards to activities of daily living (ADLs); and improving day-to-day functioning and coping strategies.

Pulmonary rehabilitation components may include assessment of the individual, education for the individual and family, breathing exercises, respiratory muscle training, general exercise and strengthening programs, nutritional interventions, psychosocial support and/or lifestyle modification. It is usually conducted in an outpatient setting.

Chronic obstructive pulmonary disease (COPD) is a diagnosis best reserved for those individuals with chronic bronchitis or emphysema who have demonstrated airflow obstruction on pulmonary function testing. Bronchial asthma is considered as a separate disorder, rather than being included under the term COPD; however, it is recognized that those with COPD may also have a component of asthma. Pulmonary rehabilitation is most useful for patients with COPD; however, certain aspects of the program may be selected for patients with other symptomatic pulmonary disorders.

Supervised pulmonary rehabilitation programs have been shown to be an effective method to control and alleviate as much as possible the symptoms and pathologic complications of respiratory impairment and to teach how to achieve optimal capability for carrying out activities of daily living in appropriately selected patients.

The 3 primary objectives of pulmonary rehabilitation services are:

- I. to control, reduce, and alleviate the symptoms and pathophysiologic complications of chronic pulmonary disease;
- II. to train the patient how to reach the highest possible level of independent functioning for his or her activities of daily living within the limitations of the pulmonary disease; and
- III. to train the patient to self-manage his or her daily living consistent with the pulmonary disease process to obtain the highest possible level of independent function.

The ideal candidate for pulmonary rehabilitation is one with moderate to moderately severe disease, stable on standard medical therapy, not distracted or limited by other serious or unstable medical conditions, willing and able to learn about his or her disease, and motivated to devote the time and effort necessary to benefit from a comprehensive care program. Patients with very mild disease may not perceive their problem as severe enough to warrant a comprehensive care program, and patients with very severe disease may be too limited to benefit appreciably. Pulmonary rehabilitation is not a primary mode of therapy for obstructive airway disease; therefore, patients should be stabilized on standard medical therapy before beginning the program.

Every pulmonary rehabilitation program is individualized for a specific patient's needs and should include a comprehensive initial evaluation, established goals, an explicit treatment plan consisting of specific modalities with the stated frequencies, anticipated duration, and periodic re-assessments at scheduled intervals. A program developed in such a manner should be documented and results of the assessments recorded.

For many years, the standard of care for pulmonary patients included inactivity and bedrest, with patients considered as passive recipients of medical treatment. The high incidence of impairment, disability, and handicap associated with COPD has led to the development of pulmonary rehabilitation programs. Such programs aim to improve the patient's ability to carry out the activities of daily living and, thereby, to improve their quality of life.

Many patients with COPD can be diagnosed, worked-up, and medically managed by their primary care physician or pulmonary specialist with resultant improvement in symptoms without the need for pulmonary rehabilitation. The goals of medical therapy are to slow the expected decline in lung function and, if possible, to improve lung function. Once the patient has been stabilized using standard medical therapy, it is unlikely that much additional improvement in pulmonary function can be expected. However, further efforts can be made by the physician to institute a rehabilitation program under his or her direction. The success of such a treatment is strongly influenced by the physician's interest and the participation of the patient and his or her family in following a program of education about the disease,

avoidance of risk factors, cessation of smoking, reduction in exposure to pulmonary irritants, immunization prophylaxis for influenza and pneumococcus, a designed exercise training program, and control of secretions, all of which can be adequately accomplished without the need for a formal pulmonary rehabilitation program. The benefits of such a pulmonary rehabilitation are most evident as changes in the quality of life. The general philosophy of a program should be to encourage patients to assume responsibility for and to become active participants and partners in taking care of themselves.

An individualized exercise program directed by the COPD patient's primary care physician or pulmonologist, focused on improving function and quality of life, can reduce respiratory symptoms and limitations and reduce hospitalizations. The exercise program should be simple and task specific (e.g., walking, dressing, etc.). A graded aerobic exercise program (e.g., walking, or bicycling, 20 mins 3 times weekly) may be helpful to prevent deterioration of physical condition and to improve the patient's ability to carry out daily activities. Pursed-lip breathing to slow the rate of breathing and abdominal breathing exercises to relieve fatigue of the accessory muscles of respiration may reduce dyspnea in some patients. A home monitoring program, in which patients are asked to record the use of metered-dose inhalers (MDI) and symptoms, is useful. A home peak flow-meter will provide an objective record of the severity of the obstruction.

Before the patient enters a formal rehabilitation program, an accurate diagnosis of COPD or other chronic pulmonary disease must be made. Lung function tests will give an indication about the physical aspects of impairment caused by the disease. The patient should have received physician-directed medical management with optimization of pulmonary function tests and still have symptoms of dyspnea which interferes with the activities of daily living and/or work. For the purposes of evaluating the extent of the physical aspects of the disability and identifying limiting factors in the gas transport chain, it is essential that the patient undergo a true maximal exercise test according to physiologic criteria.

The initial assessment or evaluation by a pulmonary therapist should include:

- I. a diagnostic work-up and evaluation of the patient's rehabilitation potential;
- II. a detailed description of specific problems the patient has in performing daily activities;
- III. chest X-ray or report review;
- IV. pulmonary function testing;
- V. exercise testing that assesses oxygen consumption and oxygenation at rest and with exercise;
- VI. indication of a high level of motivation to participate in the program;
- VII. determination of the appropriate type of care for the given pulmonary disability (e.g., select appropriate modalities, establish frequency and expected duration, etc.);
- VIII. setting of goals and objectives (e.g. improve strength, power, motion, flexibility, etc.); and
- IX. anticipation of outcomes.

The initial assessment is lengthy since the patient's functional level needs to be evaluated and measured carefully before establishing an appropriate program. As noted above, regular re-evaluations (about every 2 or 4 weeks) which are dependent on the frequency of the program and the severity of the patient's illness are required throughout the program. The purpose is to measure progression (or regression) and set new goals, frequency of treatment, and anticipated duration.

Goals should be explicit and objectively measurable, e.g., progressively improve 6- or 12-min walk. They also need to establish an appropriate length of time to achieve the anticipated outcome.

Appropriate candidates for pulmonary rehabilitation programs have pulmonary disabilities with limitation of functional status resulting in a reduction of exercise tolerance, an interference with the person's lifestyle and/or a restriction in the person's ability to perform the activities of daily living and/or work. Pulmonary rehabilitation programs are not indicated for persons whose pulmonary stress test reveals that activities are not limited by dyspnea.

Pulmonary rehabilitation programs do not benefit persons with very severe pulmonary impairment as evidenced by dyspnea at rest, difficulty in conversation (one-word answers), inability to work, cessation of most of all usual activities making him/her housebound and often limited to bed or chair with dependency upon assistance from others for most

ADLs.

Appropriate candidates should have quit smoking for at least 3 months. This act reflects the patient's motivation and active commitment to a lifestyle change. Patients who quit on the first day of the program frequently start smoking soon after the program is completed.

Candidates should have moderate to moderately severe functional pulmonary disability as evidenced by either:

- I. pulmonary function tests showing that either the FEV1, FVC, FEV1/FVC, or Dlco is less than 60 % of that predicted; or
- II. a maximal pulmonary exercise stress test under optimal bronchodilatory treatment that demonstrates a respiratory limitation to exercise with a maximal oxygen uptake (VO₂max) equal to or less than 20 ml/kg/min, or about 5 METS.

This maximal pulmonary exercise stress test test should be performed using treadmill walking or cycle ergometer with monitoring of work load, heart rate, EKG, and determinations of blood gas composition at rest and during exercise.

Appropriate candidates for pulmonary rehabilitation programs should not have any concomitant medical condition that would otherwise imminently contribute to deterioration of pulmonary status or undermine the expected benefits of the program (e.g., symptomatic coronary artery disease, congestive heart failure, myocardial infarction within the last 6 months, dysrhythmia, active joint disease, claudication, and malignancy). Candidates should not have another disabling or unstable condition which limits ability to participate fully and to concentrate on rehabilitation activities.

According to the American Association for Respiratory Care (AARC, 2002), potential contraindications to outpatient pulmonary rehabilitation include: acute cor pulmonale, ischemic cardiac disease, metastatic cancer, psychiatric disease that interferes with memory and compliance, renal failure, severe pulmonary dysfunction, severe cognitive deficit, and Significant hepatic dysfunction. The decision to provide or withhold outpatient pulmonary rehabilitation should be based on a thorough, individualized assessment.

Pulmonary rehabilitation programs are not appropriate for persons who refuse to participate, or have a strong history of medical noncompliance.

A supervised pulmonary rehabilitation program is completed once the progress notes indicate that the patient has acquired the skills to self-monitor unsupervised exercise, or documentation from progress notes indicates no potential for gain or the absence of progress in the improvement in functional capacity at any time during the program. It should be noted that improvement in arterial blood gases and pulmonary function testing is not generally expected and is not required for measuring progress in a patient participating in a pulmonary rehabilitation program.

A typical course of pulmonary rehabilitation extends for up to 6 weeks or 36 hours of therapy. Additional pulmonary rehabilitation may be considered necessary with documentation of progress in the initial 6 weeks or 36 hours of pulmonary rehabilitation; documentation that the patient's performance capacity is expected to improve; and documentation of an assessment that indicates that continuation of the supervised exercise training is necessary to enable the patient to reach an acceptable level of individual exercise tolerance consistent with the particular stage of that patient's disease.

The patient's medical record should support the pulmonary rehabilitation services being rendered. Documentation should include:

- I. a dated description of treatment received for each scheduled visit;
- II. periodic (usually at least every 5 visits) exercise testing demonstrating objective measurable findings of physical and functional status showing improvement from baseline assessments to substantiate progress achieved;
- III. periodic (usually at least every 5 visits) assessment with revision and/or re-statement of short-term goals and treatment plan;
- IV. periodic (usually bi-weekly) team conference notes of individual goals and progress;

- V. a treatment plan to attain goals with justification for continuing rehabilitation program, including frequency and duration; and
- VI. evidence of communication with referring physician.

Pulmonary rehabilitation programs are also appropriate for lung transplant candidates. For lung transplant candidates, pulmonary rehabilitation typically begins when the member is listed for transplant, and continues for 6 weeks after transplantation, at which time the member is transitioned to a home exercise program.

Spruit and Wouters (2007) stated that pulmonary rehabilitation has been demonstrated to be an important part of the management of patients with COPD. Exercise training is the corner stone of a comprehensive, multi-disciplinary pulmonary rehabilitation in COPD and has been shown to improve health-related quality of life and exercise capacity. However, not every COPD patient responds well to pulmonary rehabilitation. The authors noted that future studies should center on new modalities to conventional pulmonary rehabilitation programs to optimize its effects. These new additions include endurance training and long-acting bronchodilators; endurance training and technical modalities (e.g., inspiratory pressure support and inspiratory muscle training); interval training; resistance training; transcutaneous neuromuscular electrical stimulation; and exercise training and supplements (e.g., oxygen, oral creatine supplementation, anabolic steroids and polyunsaturated fatty acids). Currently, these new modalities of pulmonary rehabilitation have been reported to improve body composition, skeletal muscle function and sometimes exercise capacity. Nevertheless, the translation to an improved health-related quality of life is lacking, and cost-effectiveness as well as long-term effects have not been examined. Moreover, future studies should examine the effects of pulmonary rehabilitation in elderly patients with restrictive pulmonary diseases.

Nici (2008) noted that benefits derived from comprehensive pulmonary rehabilitation, when applied to patients who have lung cancer, should have significant impact on both survival and health status. Because pulmonary rehabilitation is known to improve exercise capacity, it is reasonable to expect that this treatment modality may provide more patients with a potential cure. In addition, improvement in symptoms and quality of life can prove critically important when long-term survival is not an outcome that can be impacted on. Studies thus far support the value of this treatment modality in the global approach to patients who have lung cancer. The author stated that future well-designed clinical trials will need to corroborate these findings.

In a prospective, randomized, controlled study, Eaton et al (2009) determined if early pulmonary rehabilitation, commenced as an inpatient and continued after discharge, reduced acute health-care utilization. Consecutive COPD patients (n = 397), admitted with an exacerbation, were screened: 228 satisfied the eligibility criteria, of whom 97 consented to randomization to rehabilitation or usual care. Both intention-to-treat and per-protocol analyses were reported with adherence being defined a priori as participation in at least 75 % of rehabilitation sessions. Participants were elderly with severe impairment of pulmonary function, poor health-related quality of life and high COPD-related morbidity. The rehabilitation group demonstrated a 23 % (95 % confidence interval [CI]: 11 to 36 %) risk of re-admission at 3 months, with attendees having a 16 % (95 % CI: 0 to 32 %) risk compared with 32 % (95 % CI: 19 to 45 %) for usual care. These differences were non-significant. There were a total of 79 COPD-related re-admission days (1.7 per patient, 95 % CI: 0.6 to 2.7, p = 0.19) in the rehabilitation group, compared with 25 (1.3 per patient, 95 % CI: 0 to 3.1, p = 0.17) for the attendees and 209 (4.2 per patient, 95 % CI: 1.7 to 6.7) for usual care. The body mass index, airflow obstruction, dyspnea and exercise capacity index showed a non-significant trend to greater improvement among attendees compared with those receiving usual care (5.5 (2.3) and 5.6 (2.7) at baseline, improving to 3.7 (1.9) and 4.5 (2.5), respectively, at 3 months). No adverse effects were identified. The authors concluded that early inpatient-outpatient rehabilitation for COPD patients admitted with an exacerbation was feasible and safe, and was associated with a non-significant trend towards reduced acute health-care utilization.

In a Cochrane review, Puhan et al (2009) evaluated the effects of pulmonary rehabilitation following COPD exacerbations on future hospital admissions (primary outcome) and other patient-important outcomes (mortality, health-related quality of life and exercise capacity). Randomized controlled trials comparing pulmonary rehabilitation of any duration after exacerbation of COPD with conventional care were selected. Pulmonary rehabilitation programs needed to include at least physical exercise. Control groups received conventional community care without rehabilitation. These researchers calculated pooled odds ratios (ORs) and weighted mean differences (WMD) using fixed-effects models. They requested missing data from the authors of the primary studies. A total of 6 trials (n = 219) were

identified. Pulmonary rehabilitation significantly reduced hospital admissions (pooled OR 0.13 [95 % CI: 0.04 to 0.35], number needed to treat (NNT) 3 [95 % CI: 2 to 4], over 34 weeks) and mortality (pooled OR 0.29 [95 % CI: 0.10 to 0.84], NNT 6 [95 % CI: 5 to 30] over 107 weeks). Effects of pulmonary rehabilitation on health-related quality of life were well above the minimal important difference (WMD for dyspnea, fatigue, emotional function, and mastery domains of the Chronic Respiratory Questionnaire between 1.15 (95 % CI: 0.94 to 1.36) and 1.88 (95 % CI: 1.67 to 2.09) and between -9.9 (95 % CI: -18.05 to -1.73) and -17.1 (95 % CI: -23.55 to -10.68) for total, impact and activity limitation domains of the St. Georges Respiratory Questionnaire). In all trials, pulmonary rehabilitation improved exercise capacity (60 to 215 meters in 6-min or shuttle walk tests). No adverse events were reported (2 studies). The authors concluded that evidence from small studies of moderate methodological quality suggested that pulmonary rehabilitation is a highly effective and safe intervention to reduce hospital admissions and mortality and to improve health-related quality of life in COPD patients after suffering an exacerbation.

Shannon (2010) stated that over the last decade, evidence-based support for pulmonary rehabilitation in the management of patients with chronic lung disease has grown tremendously. A beneficial role of pulmonary rehabilitation has been largely shown among patients with COPD and in patients with pulmonary emphysema enlisted for lung volume reduction surgery. In these settings, significant reductions in dyspnea, and improvements in exercise performance and health-related quality of life have been clearly demonstrated following a program of pulmonary rehabilitation. Pulmonary rehabilitation is often advocated as an adjunctive intervention in patients with cancer; however, the benefits of this intervention in the cancer setting, particularly in the peri-operative setting for lung cancer, are only recently emerging. The author summarized these investigations and highlighted ongoing controversies regarding the utility of pulmonary rehabilitation in the surgical and medical management of patients with lung cancer. Recent small studies suggest that pulmonary rehabilitation may favorably impact lung cancer management by improving a variety of clinically meaningful outcomes such as performance status, chemotherapy-related fatigue, oxygen consumption, exercise tolerance, and health-related quality of life. These findings, although intriguing, have not been investigated in any large, controlled trials to determine their impact, if any, on surgical resectability and outcome or on tolerance to aggressive chemo-radiation therapy regimens. The author concluded that pulmonary rehabilitation shows promise as a therapeutic intervention in the management of lung cancer; however, well-designed, adequately powered studies are needed to examine outstanding questions regarding its exact role in guiding lung cancer management.

An official statement of the American College of Physicians (ACP), American College of Chest Physicians (ACCP), American Thoracic Society (ATS), and European Respiratory Society (ERS) (Qaseem et al, 2011) represents an update of the 2007 ACP clinical practice guideline on diagnosis and management of stable COPD and is intended for clinicians who manage patients with COPD. The ACP, ACCP, ATS, and ERS recommend that clinicians should prescribe pulmonary rehabilitation for symptomatic patients with an FEV(1) less than 50 % predicted (Grade: Strong recommendation, moderate-quality evidence). Clinicians may consider pulmonary rehabilitation for symptomatic or exercise-limited patients with an FEV(1) greater than 50 % predicted (Grade: Weak recommendation, moderate-quality evidence).

Schmidt-Hansen et al (2012) stated that the preferred treatment for lung cancer is surgery if the disease is considered resectable and the patient is considered surgically fit. Pre-operative smoking cessation and/or pre-operative pulmonary rehabilitation might improve post-operative outcomes after lung cancer surgery. The objectives of this systematic review were to determine the effectiveness of

- I. pre-operative smoking cessation and
- II. pre-operative pulmonary rehabilitation on peri- and post-operative outcomes in patients who undergo resection for lung cancer.

These investigators searched MEDLINE, PreMedline, Embase, Cochrane Library, Cinahl, BNI, Psychinfo, Amed, Web of Science (SCI and SSCI), and Biomed Central. Original studies published in English investigating the effect of pre-operative smoking cessation or pre-operative pulmonary rehabilitation on operative and longer-term outcomes in greater than or equal to 50 patients who received surgery with curative intent for lung cancer were included. Of the 7 included studies that examined the effect of pre-operative smoking cessation (n = 6) and pre-operative pulmonary rehabilitation (n = 1) on outcomes after lung cancer surgery, none was randomized controlled trials and only 1 was prospective. The studies used different smoking classifications, the baseline characteristics differed between the study groups in some of

the studies, and most had small sample sizes. No formal data synthesis was therefore possible. The included studies were marked by methodological limitations. On the basis of the reported bodies of evidence, it is not possible to make any firm conclusions about the effect of pre-operative smoking cessation or of pre-operative pulmonary rehabilitation on operative outcomes in patients undergoing surgery for lung cancer.

In a pilot, randomized, single-blinded study, Morano et al (2013) examined the effect of 4 weeks of pulmonary rehabilitation (PR) versus chest physical therapy (CPT) on the pre-operative functional capacity and post-operative respiratory morbidity of patients (n = 24) undergoing lung cancer resection. Patients were randomly assigned to receive PR (strength and endurance training) versus CPT (breathing exercises for lung expansion). Both groups received educational classes. Main outcome measures were functional parameters assessed before and after 4 weeks of PR or CPT (phase 1), as well as pulmonary complications assessed after lung cancer resection (phase 2). A total of 12 patients were randomly assigned to the PR arm and 12 to the CPT arm. Three patients in the CPT arm were not submitted to lung resection because of inoperable cancer. During phase 1 evaluation, most functional parameters in the PR group improved from baseline to 1 month: FVC (1.47 L [1.27 to 2.33 L] versus 1.71 L [1.65 to 2.80 L], respectively; p = 0.02); percentage of predicted FVC (FVC %; 62.5 % [49 % to 71 %] versus 76 % [65 % to 79.7 %], respectively; p < 0.05); 6-minute walk test (425.5 ± 85.3 m versus 475 ± 86.5m, respectively; p < 0.05); maximal inspiratory pressure (90 ± 45.9 cm H₂O versus 117.5 ± 36.5 cm H₂O, respectively; p < 0.05); and maximal expiratory pressure (79.7 ± 17.1 cm H₂O versus 92.9 ± 21.4 cm H₂O, respectively; p < 0.05). During phase 2 evaluation, the PR group had a lower incidence of post-operative respiratory morbidity (p = 0.01), a shorter length of post-operative stay (12.2 ± 3.6 days versus 7.8 ± 4.8 days, respectively; p = 0.04), and required a chest tube for fewer days (7.4 ± 2.6 days versus 4.5 ± 2.9 days, respectively; p = 0.03) compared with the CPT arm. The authors concluded that these findings suggested that 4 weeks of PR before lung cancer resection improved pre-operative functional capacity and decreased the post-operative respiratory morbidity. The findings from this small pilot study need to be validated by well-designed studies.

In a Cochrane review, Dowman and colleagues (2014) examined if PR in patients with interstitial lung disease (ILD) has beneficial effects on exercise capacity, symptoms, quality of life and survival compared with no pulmonary rehabilitation in patients with ILD. These investigators searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2014, Issue 6), MEDLINE (Ovid), EMBASE (Ovid), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO) and the Physiotherapy Evidence Database (PEDro) (all searched from inception to June 2014). They also searched the reference lists of relevant studies, international clinical trial registries and respiratory conference abstracts to look for qualifying studies. Randomized and quasi-randomized controlled trials in which pulmonary rehabilitation was compared with no pulmonary rehabilitation or with other therapy in people with ILD of any origin were included. Two review authors independently selected trials for inclusion, extracted data and assessed risk of bias. Study authors were contacted to provide missing data and information regarding adverse effects. A priori subgroup analyses were specified for participants with idiopathic pulmonary fibrosis (IPF) and participants with severe lung disease (low diffusing capacity or desaturation during exercise). These researchers planned to subgroup according to training modality applied, but there were insufficient data. A total of 9 studies were included, 6 of which were published as abstracts. Five studies were included in the meta-analysis (86 participants who undertook PR and 82 control participants). One study used a blinded assessor and intention-to-treat analysis. No adverse effects of PR were reported. Pulmonary rehabilitation improved the 6-minute walk distance with weighted mean difference (WMD) of 44.34 meters (95 % CI: 26.04 to 62.64 meters) and improved oxygen consumption (VO₂) peak with WMD of 1.24 ml/kg/min-1 (95 % CI 0.46 to 2.03 ml/kg/min-1). Improvements in 6-minute walk distance and VO₂ peak were also seen in the subgroup of participants with IPF (WMD 35.63 meters, 95 % CI: 16.02 to 55.23 meters; WMD 1.46 ml/kg/min-1, 95 % CI: 0.54 to 2.39 ml/kg/min-1, respectively). Reduced dyspnea (standardized mean difference (SMD) -0.66, 95 % CI: -1.05 to -0.28) following PR was also seen in the IPF subgroup (SMD -0.68, 95 % CI: -1.12 to -0.25). Quality of life improved following PR for all participants on a variety of measures (SMD 0.59, 95 % CI: 0.20 to 0.98) and for the subgroup of people with IPF (SMD 0.59, 95 % CI: 0.14 to 1.03). Two studies reported longer-term outcomes, with no significant effects of PR on clinical variables or survival at 3 or 6 months. Available data were insufficient to allow examination of the impact of disease severity or exercise training modality. The authors concluded that PR seemed to be safe for people with ILD. Improvements in functional exercise capacity, dyspnea and quality of life are seen immediately following PR, with benefits also evident in IPF. However, because of inadequate reporting of methods and small numbers of included participants, the quality of evidence was low to moderate. Moreover, little evidence was available regarding longer-term effects of PR.

Individuals with COPD and Mild Symptoms:

Rugbjerg et al (2015) stated that most guidelines recommend PR for patients with COPD and modified Medical Research Council dyspnea scale (mMRC) levels greater than or equal to 2, but the effectiveness of PR in patients with less advanced disease is not well established. These researchers investigated the effects of PR in patients with COPD and mMRC less than or equal to 1. The methodology was developed as a part of evidence-based guideline development and is in accordance with the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group. These investigators identified randomized controlled trials (RCTs) through a systematic, multi-database literature search and selected RCTs comparing the effects of PR with usual care in patients with COPD and mMRC less than or equal to 1. Predefined critical outcomes were health-related quality of life (HRQoL), adverse effects and mortality, while walking distance, maximal exercise capacity, muscle strength, and drop-outs were important outcomes. Two authors independently extracted data, assessed trial eligibility and risk of bias, and graded the evidence. Meta-analyses were performed when deemed feasible. A total of 4 RCTs (489 participants) were included. On the basis of moderate-quality evidence, these investigators found a clinically and statistically significant improvement in short-term HRQoL of 4.2 units (95 % CI: -4.51 to -3.89) on St George's Respiratory Questionnaire, but not at the longest follow-up. They also found a statistically significant improvement of 25.71 m (95 % CI: 15.76 to 35.65) in the 6-minute walk test with PR; however, this improvement was not considered clinically relevant. No difference was found for mortality, and insufficient data prohibited meta-analysis for muscle strength and maximal exercise capacity. No adverse effects were reported. The authors concluded that they found a moderate quality of evidence suggesting a small, significant improvement in short-term HRQoL and a clinically non-significant improvement in walking distance following PR in patients with COPD and mild symptoms. This resulted in a weak recommendation of routine PR in these patients using the GRADE approach.

Prevention of Acute Exacerbations of COPD in Persons with Moderate, Severe, or Very Severe COPD:

The American College of Chest Physicians and Canadian Thoracic Society guideline on “Prevention of acute exacerbations of COPD” (Criner et al, 2015) states that in patients with moderate, severe, or very severe COPD who have had an exacerbation greater than the past 4 weeks, the panel does not suggest PR to prevent acute exacerbations of COPD.

Non-Cystic Fibrosis Bronchiectasis:

In a systematic review, Lee and colleagues (2017) examined the effect of PR (exercise and education) or exercise training (ET) on exercise capacity, health-related quality of life (HRQOL), symptoms, frequency of exacerbations, and mortality compared with no treatment in adults with non-cystic fibrosis bronchiectasis. Computer-based databases were searched from their inception to February 2016; RCTs of PR or ET versus no treatment in adults with bronchiectasis were included. Two reviewers independently extracted data and assessed methodological quality using the Cochrane risk-of-bias tool. A total of 4 trials with 164 participants were included, with variable study quality. Supervised out-patient PR or ET of 8 weeks improved incremental shuttle walk distance (WMD = 67 m; 95 % CI: 52 to 82 m) and disease-specific HRQOL (WMD = -4.65; 95 % CI: -6.7 to -2.6 units) immediately after intervention, but these benefits were not sustained at 6 months. There was no effect on cough-related quality of life (WMD = 1.3; 95 % CI: -0.9 to 3.4 units) or psychological symptoms. Pulmonary rehabilitation commenced during an acute exacerbation and continued beyond discharge had no effect on exercise capacity or HRQOL. The frequency of exacerbations over 12 months was reduced with out-patient ET (median of 2 versus 1; $p = 0.013$), but PR initiated during an exacerbation had no impact on exacerbation frequency or mortality. The authors concluded that short-term improvements in exercise capacity and HRQOL were achieved with supervised PR and ET programs, but sustaining these benefits is challenging in people with bronchiectasis. They stated that the frequency of exacerbations over 12 months was reduced with ET only.

Sarcoidosis:

Lingner and associates (2015) stated that available data assessing the effectiveness of PR for patients with chronic

sarcoidosis are scant; for Germany, there are none at all. To gain information about the benefit of in-house PR for patients with chronic sarcoidosis and for the health care system, these investigators intended to collect data in a prospective multi-center "real-life" cohort trial -- Prospective Catamnesis Study of Sarcoidosis in Pulmonary Rehabilitation -- will evaluate a multi-modal 3-week inpatient PR program for adult patients with chronic sarcoidosis over a 1-year follow-up time. Defined specific clinical measurements and tests will be performed at the beginning and the end of the rehabilitation. In addition, questionnaires concerning HRQOL and the patients' symptoms will be provided to all patients. Inclusion criteria will be referral to 1 of the 6 participating PR clinics in Germany for sarcoidosis and age between 18 and 80 years. Patients will only be excluded for a lack of German language skills or the inability to understand and complete the study questionnaires. To rule out seasonal influences, the recruitment will take place over a period of 1 year. In total, at least 121 patients are planned to be included. A descriptive statistical analysis of the data will be performed, including multivariate analyses. The primary outcomes are specific HRQOL (St George's Respiratory Questionnaire) and exercise capacity (6-minute walk test). The secondary outcomes are several routine lung function and laboratory parameters, dyspnea scores and blood gas analysis at rest and during exercise, changes in fatigue, psychological burden, and generic HRQOL (36-item Short Form Health Survey). Funding was obtained on October 12, 2010; enrollment began on January 15, 2011 and was completed by January 14, 2012. Results are anticipated late summer 2015. The authors concluded that due to the large number of participants, they expect to obtain representative findings concerning the effectiveness of PR for patients with sarcoidosis and to provide a dataset of assessed objective and subjective short- and long-term changes due to PR. They stated that the results should form the basis for the planning of a RCT.

Prevention of Acute Exacerbations of COPD in Persons with Moderate, Severe, or Very Severe COPD:

Moore and colleagues (2017) noted that in previous systematic reviews (predominantly of RCTs), PR has been shown to reduce hospital admissions for acute exacerbations of COPD (AECOPD). However, findings have been less consistent for cohort studies. These investigators compared rates of hospitalized and general practice (GP)-treated AECOPD prior to and following PR. Using anonymized data from the Clinical Practice Research Datalink and Hospital Episode Statistics, hospital admissions and GP visits for AECOPD were compared 1 year prior to and 1 year following PR in patients referred for PR. Exacerbation rates were also compared between individuals eligible and referred for PR vs those eligible and not referred. A total of 69,089 (64 %) of the patients with COPD in the cohort were eligible for PR. Of these, only 6,436 (9.3 %) were recorded as having been referred for rehabilitation. A total of 62,019 (89.8 %) were not referred, and 634 (0.98 %) declined referral. When combining GP and hospital exacerbations, patients who were eligible and referred for PR had a slightly higher but not statistically significant exacerbation rate (2.83 exacerbations/patient-year; 95 % CI: 2.66 to 3.00) than those who were eligible but not referred (2.17 exacerbations/patient-year; 95 % CI: 2.11 to 2.24). The authors concluded that the findings of this study showed that less than 10 % of patients who were eligible for PR were actually referred. Patients who were eligible and referred for (but not necessarily completed) PR did not have fewer GP visits and hospitalizations for AECOPD in the year following PR compared with those not referred or compared with the year prior to PR.

Table: CPT Codes / HCPCS Codes / ICD-10 Codes

| Code | Code Description |
|-------------|-------------------------|
|-------------|-------------------------|

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

Other CPT codes related to the CPB:

| | |
|---------------|---|
| 78580 - 78599 | Diagnostic radiology, (eg, particulates) respiratory system |
| 94010 - 94799 | Pulmonary laboratory medicine |

HCPCS codes covered if selection criteria are met:

| | |
|-------|--|
| G0237 | Therapeutic procedures to increase strength or endurance of respiratory muscles, face-to-face, one-on-one, each 15 minutes (includes monitoring) |
| G0238 | Therapeutic procedures to improve respiratory function, other than described by G0237, one-on-one, face-to-face, per 15 minutes (includes monitoring) |
| G0239 | Therapeutic procedures to improve respiratory function or increase strength or endurance of respiratory muscles, 2 or more individuals (includes monitoring) |
| G0424 | Pulmonary rehabilitation, including exercise (includes monitoring) one hour, per session, up to two sessions per day |
| S9473 | Pulmonary rehabilitation program, non-physician provider, per diem |

Other HCPCS codes related to the CPB:

| | |
|-------|--------------------|
| A9300 | Exercise equipment |
|-------|--------------------|

ICD-10 codes covered if selection criteria are met:

| | |
|-----------------|--|
| D86.0 - D86.9 | Sarcoidosis |
| E84.0 - E84.9 | Cystic fibrosis |
| E88.01 | Alpha-1-antitrypsin deficiency |
| G65.0 - G65.2 | Sequelae of inflammatory and toxic polyneuropathies |
| G70.00 - G70.9 | Myasthenia gravis and other myoneural disorders |
| G71.0 - G71.9 | Primary disorders of muscles |
| G72.0 - G72.9 | Other and unspecified myopathies |
| J40 - J47.9 | Chronic lower respiratory diseases |
| J60 - J70.9 | Lung diseases due to external agents |
| J80 - J84.9 | Other respiratory diseases principally affecting the interstitium |
| J85.0 - J86.9 | Suppurative necrotic conditions of the lower respiratory track |
| M41.00 - M41.9 | Scoliosis |
| M45.0 - M45.9 | Ankylosing spondylitis |
| P27.0 - P27.9 | Chronic respiratory disease originating in the perinatal period [bronchopulmonary dysplasia, pulmonary fibrosis] |
| R06.00 - R06.09 | Dyspnea [at rest or with exertion] |
| Z76.82 | Awaiting organ transplant status [when patient is listed for transplant] |
| Z94.2 | Lung transplant status |

ICD-10 codes contraindicated for this CPB:

| | |
|-------------------|---|
| C00.0 - C96.9 | Malignant neoplasm [not covered for pre-operative pulmonary rehabilitation] |
| F17.200 - F17.299 | Nicotine dependence [recent or has quit for less than 3 months] |
| I21.01 - I22.9 | ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction [within last 6 months] |
| I21.A1 | Myocardial infarction type 2 |
| I21.A9 | Other myocardial infarction type |
| I25.10 - I25.9 | Chronic ischemic heart disease [symptomatic] |
| I47.0 - I49.9 | Paroxysmal tachycardia, atrial fibrillation and flutter and other cardiac arrhythmias |

| | |
|----------------|---|
| I50.20 - I50.9 | Heart failure |
| I73.89 - I73.9 | Other specified and unspecified peripheral vascular disease [claudication] |
| I82.0 - I82.91 | Other venous embolism and thrombosis [claudication] |
| M00.00 - M25.9 | Arthropathies [active] |
| Z87.891 | Personal history of nicotine dependence [recent or has quit for less than 3 months] |

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Policy History

- [Last Review](#) 

Effective: 07/21/1995

Next Review: 01/10/2019

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

Additional Information

- [Clinical Policy Bulletin Notes](#)

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Section 7.0

Coverage Guidances

Newer Interventional Procedures for GERD

Draft Coverage Guidance for VbBS Consideration

January 17, 2019

Background

- Gastroesophageal reflux disease (GERD) is a long-lasting and more serious form of gastroesophageal reflux
 - The lower esophageal sphincter becomes weak or relaxes, allowing stomach contents to rise up into the esophagus
 - Common symptoms of GERD include heartburn, bad breath, nausea, pain in the chest or upper part of the abdomen, painful swallowing, and vomiting
 - Patients with GERD can sometimes breathe stomach acid into the lungs, provoking asthma, laryngitis, or pneumonia
 - GERD can also cause Barrett's esophagus, a precursor of esophageal adenocarcinoma

Background

- An estimated 20% of the U.S. population has GERD
- Populations at higher risk for GERD include:
 - People who are overweight
 - Pregnant women
 - People who smoke or are exposed to secondhand smoke
 - People taking certain medicines (e.g., calcium channel blockers, antihistamines, sedatives, antidepressants, asthma medications, pain medications)
- Procedures sometimes used in the evaluation of GERD include upper gastrointestinal endoscopy and biopsy, x-rays of the upper gastrointestinal area, and esophageal pH and impedance monitoring

Background

- Lifestyle changes may improve or eliminate GERD:
 - Not overeating
 - Not eating 2 to 3 hours before sleeping
 - Quitting smoking and avoiding secondhand smoke
 - Wearing loose-fitting clothing around the abdomen
 - Sleeping on a bed that is on a slight angle
- Prescription and nonprescription medicines to treat GERD:
 - Antacids
 - Histamine 2 receptor antagonists
 - Proton pump inhibitors (PPI)
 - Prokinetic agents

Background

- Most common surgery for GERD is laparoscopic fundoplication
 - Top of the stomach is sewed around the esophagus to add pressure to the lower end of the esophagus and reduce reflux
 - Performed under general anesthesia, and most patients return to usual activities in 2 to 3 weeks
- The focus of this coverage guidance is 2 additional treatments for GERD:
 - Transoral incisionless fundoplication (TIF)
 - Magnetic sphincter augmentation (MSA)

Background

- Transoral incisionless fundoplication (TIF)
 - Minimally invasive, endoscopic technique to restore the valve at the gastroesophageal junction via endoluminal fundoplication
 - EsophyX[®] device is a fastener delivery system designed to reconstruct the gastroesophageal valve and help restore its function as a reflux barrier
 - Approximately 20 fasteners are implanted during the procedure to create fusion of the esophageal and fundus tissues and form the valve
 - First iteration (TIF 1.0) creates the fundoplication wrap around the gastroesophageal junction
 - Later version of the procedure (TIF 2.0) creates the wrap around the intraabdominal portion of the esophagus
 - Indications for TIF include intractable GERD symptoms, no or mild esophagitis with hiatal hernia < 2 cm, and abnormal acid reflux

Background

- Magnetic sphincter augmentation (MSA)
 - MSA is performed using the LINX Reflux Management System, approved by the FDA in 2012
 - Small, flexible ring of interlinked titanium beads with magnetic cores placed around the esophagus just above the stomach
 - Sizing tool is used to determine the appropriate size LINX System, and the device is positioned using sutures
 - Magnetic attraction between the beads helps the lower esophageal sphincter resist opening because of gastric pressures; swallowing temporarily breaks the magnetic bonds, allowing food and liquid to pass normally
 - Indicated for patients diagnosed with GERD as defined by abnormal pH testing, and who continue to have chronic GERD symptoms despite maximum therapy

Scope Statement

- Populations
 - Adults with GERD
- Interventions
 - Transoral incisionless fundoplication
 - Laparoscopic magnetic ring procedure for augmentation of the lower esophageal sphincter
- Comparators
 - Medical management
 - Nissen fundoplication
 - Interventions compared to each other
 - Sham interventions

Scope Statement

- Critical Outcomes
 - Incident Barrett's esophagus
 - Complications of GERD (e.g., stricture)
- Important Outcomes
 - GERD symptom scores
 - Change in PPI therapy
 - Harms (e.g., repeat interventions)

Scope Statement

Key Questions

1. What is the comparative effectiveness of MSA of the lower esophageal sphincter and TIF in the treatment of GERD?
2. How does the effectiveness of MSA of the lower esophageal sphincter and TIF in the treatment vary by:
 - a. Patient characteristics (e.g., age, gender, weight, tobacco use)
 - b. Comorbid conditions
 - c. Duration of symptoms
 - d. Response to prior treatments
 - e. Procedural technique
3. What are the harms of MSA of the lower esophageal sphincter and TIF in the treatment of GERD?

Evidence Sources: TIF

- Huang et al., 2017
 - Systematic review and meta-analysis of trials using TIF compared to sham procedure or PPI therapy
- Richter et al., 2018
 - Network meta-analysis of TIF, laparoscopic Nissen fundoplication, and PPI therapy

Evidence Review: TIF

- Huang et al., 2017
 - Good-quality systematic review and meta-analysis
 - 5 RCTs (n = 343) using TIF 2.0; comparator was sham procedure in 2 RCTs and PPI therapy in 3 RCTs
 - RCTs mainly low to moderate risk of bias
 - Primary outcome measure was treatment response at 6 months, defined as:
 - Improvement of at least 50% in the GERD health-related quality of life score, or remission of heartburn and regurgitation, or complete cessation of PPI therapy; considered hierarchically

Evidence Review: TIF

- Huang et al., 2017
 - Meta-analysis of treatment response at 6 months
 - Treatment response was significantly higher in TIF groups compared to control groups (66% vs. 30%, RR 2.44, 95% CI 1.44 to 4.79, $p = 0.02$, $I^2 = 70\%$)
 - Prospective observational studies indicated that treatment response to TIF appears to be sustained through 36 months, but then begins to decline (estimates beyond 36 months are based on very small numbers of patients)
 - PPI use in prospective observational studies shows a sustained effect between 12 and 36 months (cessation rate of approximately 60%), but PPI cessation beyond 36 months falls to 30-50%

Evidence Review: TIF

- Huang et al., 2017
 - Adverse events analyzed in 16 studies: 4 RCTs and 12 observational studies
 - 19 serious adverse events among 781 patients who received the TIF procedure (2.4%) including
 - 7 perforations
 - 5 episodes of bleeding
 - 4 pneumothoraces
 - 1 death (reported 20 months after the TIF procedure)

Evidence Review: TIF

- Richter et al., 2018
 - Network meta-analysis included:
 - No RCTs directly comparing TIF with laparoscopic Nissen fundoplication (LNF)
 - 120 patients in the TIF vs. PPI trials
 - 835 patients in the LNF vs. PPI trials
 - Outcome was GERD health-related quality of life
 - TIF had the greatest probability of being the best treatment (surface under the cumulative ranking curve of 0.92) followed by LNF (surface under the cumulative ranking curve of 0.66)
 - Pairwise comparison of TIF and LNF was not statistically significant (OR 2.08, 95% CI 0.71 to 6.09)
 - Quality of evidence was judged to be very low

Evidence Review: TIF

- Richter et al., 2018
 - Authors of this study queried the MAUDE database for reports on the TIF procedure and found (out of an unknown denominator of total TIF procedures)
 - 50 cases of device malfunction
 - 75 cases of injury including
 - 36 perforations
 - 10 gastrointestinal bleeds
 - 8 esophageal lacerations
 - 8 pleural effusions
 - 6 mediastinal abscesses

Evidence Summary: TIF

- There is no evidence that TIF reduces the rate of incident Barrett's esophagus or complications of GERD (e.g., stricture)
- There is low-certainty evidence that TIF improves treatment response compared with sham procedures and/or PPI, but the durability of that improvement beyond 36 months is less certain
- Many patients who underwent TIF were able to stop PPI treatment
- The overall rate of adverse effects with TIF is approximately 2.5% in the studies
- There are no direct randomized comparisons of TIF and laparoscopic fundoplication, but a network meta-analysis suggested there was no statistically significant difference between the 2 procedures in improving GERD health-related quality of life

GRADE Table: TIF

| Outcomes | Estimate of Effect for Outcome/ Confidence in Estimate |
|--|---|
| Incident Barrett's esophagus (Critical outcome) | No data |
| Complications of GERD (e.g., stricture) (Critical outcome) | No data |

GRADE Table: TIF

| Outcomes | Estimate of Effect for Outcome/ Confidence in Estimate |
|--|---|
| GERD symptom scores (Important outcome) | <p>Treatment response at 6 months: 124/188 (66%) for intervention vs. 32/105 (30%) for control/sham ARD = 36% NNT = 2-3 RR 2.44 (95% CI 1.44 to 1.79, p = 0.02) ●●○○ (Low confidence, based on 4 RCTs, n = 293)</p> |
| Change in PPI therapy (Important outcome) | <p>At 6 months, approximately 70% of patients reported PPI cessation ●●○○ (Low confidence, based on 9 observational studies, n = 439)</p> |
| Harms (Important outcome) | <p>Overall rate of serious adverse events was 2.4% ●●○○ (Low confidence, based on 12 observational studies and 4 RCTs, n = 781)</p> |

Payer Policies: TIF

- Washington State Medicaid Program
 - No Washington Medicaid coverage policy was found for TIF
- Medicare
 - No National Coverage Determinations were found for TIF
 - 2 Local Coverage Determination provide coverage for TIF under certain conditions, such as
 - Symptoms must not be completely responsive to PPI as judged by GERD HRQL scores of ≤ 12 while on PPI and ≥ 20 when off for 14 days
 - Hiatal hernia ≤ 2 cm, if present
 - BMI ≤ 35 , esophagitis LA grade $\leq B$, Barrett's esophagus ≤ 2 cm

Payer Policies: TIF

- Private payers
 - Aetna, Cigna, and Regence do not provide coverage for TIF
 - Moda provides coverage for TIF when a number of conditions are met, including:
 - Confirmed diagnosis of esophageal reflux by endoscopy, ambulatory pH, or barium swallow testing
 - GERD symptoms for 1 year occurring 2 to 3 times per week
 - BMI \leq 35
 - History of daily PPI therapy for greater than 6 months
 - Absence of a hiatal hernia or 1 that is 2 cm or less
 - No esophagitis LA grade C or D
 - No Barrett's esophagus, or if present it is 2 cm or less
 - No achalasia, esophageal ulcer, or esophageal motility disorder
 - No previous failed anti-reflux surgery/procedure

Guidelines: TIF

- 2 guidelines were identified:
 - American College of Gastroenterology
 - TIF cannot be recommended as an alternative to medical or traditional surgical therapy
 - European Association of Endoscopic Surgery
 - Not enough evidence available to recommend an alternative option to laparoscopic fundoplication for severe GERD

Public Comment

- Public comments on TIF submitted by EndoGastric Solutions, manufacturer of the EsophyX[®] TIF device
 - Comment: Indications for use of TIF should be based on indications in FDA approval
 - Response: Our recommendations for TIF indications are based on the published literature as well as the policies of other insurers
 - Comment: RCTs of TIF used only EsophyX[®], so coverage guidance should only recommend EsophyX[®] and not other devices
 - Response: Coverage guidance revised to specify that EsophyX[®] is the only device identified in the evidence reviewed for this coverage guidance

Discussion: TIF

Values and Preferences

For patients with chronic GERD symptomatology, we would expect values and preferences to be highly variable between medical and surgical treatment options, depending on the severity of symptoms and disease complications. Most patients with symptomatic control on chronic PPI therapy would prefer to continue medical management, although some would choose surgery to avoid possible long-term harm associated with PPIs. GERD patients for whom PPI therapy isn't working or is needed twice daily would value surgical intervention if safe and effective. Many would prefer TIF as a less invasive procedure, but others would prefer the laparoscopic Nissen or Toupe procedures as better established.

Discussion: TIF

Resource Allocation

Professional fees for the TIF procedure are generally lower than the fees for laparoscopic surgical procedures, but when facility and ancillary costs are taken into account, the difference in total procedure costs may not be significant.

If lesser degrees of GERD severity are treated with TIF rather than chronic medical therapy, surgical treatment costs for the covered population will rise as TIF utilization increases. The magnitude of offsetting savings in PPI or other medical therapy will vary, depending on the pricing of generic and brand name drugs.

Discussion: TIF

Balance of Benefits and Harms

Based on low-certainty evidence, the TIF procedure using the EsophyX[®] device appears to be effective in improving GERD-related quality of life and reducing or eliminating the need for chronic PPI therapy. There is no evidence that TIF reduces the rate of incident Barrett's esophagus or complications of GERD (e.g., stricture). Serious adverse effects (including perforation, bleeding, and pneumothorax) do occur with TIF, but the overall 2.4% rate of these events suggests that, on balance, the benefits of TIF outweigh the harms.

Discussion: TIF

Rationale

Although there is no evidence directly comparing TIF with laparoscopic fundoplication procedures, overall the two surgical approaches appear to have similar effectiveness. Coverage of the TIF procedure will not significantly change resource allocation for GERD management, and values and preferences would favor inclusion of TIF coverage, especially as an option for GERD patients whose symptoms are not controlled on chronic medical therapy. Current published evidence supports the safety and efficacy of the EsophyX[®] device used in this procedure. EsophyX[®] was the only device included in the systematic reviews and randomized trials that were identified for this coverage guidance. Other TIF devices and systems are not recommended for coverage because there are no comparative data. Our recommendation to cover the TIF procedure is weak because of our low level of confidence in the evidence.

Discussion: TIF

Transoral incisionless fundoplication is recommended for coverage of GERD treatment only when the following criteria are met (*weak recommendation*):

- 18 years of age or older
- Confirmed diagnosis of esophageal reflux by endoscopy, ambulatory pH, or barium swallow testing
- History of GERD symptoms for one year, occurring at least two to three times per week in the past month
- History of daily proton pump inhibitor therapy for the most recent six months
- Body mass index (BMI) ≤ 35
- Absence of all of the following conditions (*see next slide*)

Discussion: TIF

- Absence of all of the following conditions:
 - Hiatal hernia larger than 2 cm
 - Esophagitis with LA grade of C or D
 - Barrett's esophagus greater than 2 cm
 - Achalasia
 - Esophageal ulcer
 - Esophageal motility disorder
 - Altered esophageal anatomy preventing insertion of the device
 - Previous failed anti-reflux surgery or procedure

EsophyX[®] was the only device identified in the evidence reviewed for this coverage guidance. Other transoral fundoplication devices or systems are not recommended for coverage.

For patients who have recurrent symptoms or fail the initial TIF procedure, repeat TIF is not recommended for coverage (*strong recommendation*).

Evidence Sources: MSA

- Aiolfi et al., 2018
 - Fair-quality systematic review and meta-analysis of 7 observational studies (n = 1,211) comparing MSA with laparoscopic fundoplication using Nissen or Toupe techniques
- Bell et al., 2019
 - Poor-quality RCT of MSA compared to PPI therapy (n = 152)

Evidence Review: MSA

- Aiolfi et al., 2018
 - No statistically significant differences:
 - GERD health-related quality of life score at 6 to 12 months (MD -0.48, 95% CI -1.05 to 0.09, $p = 0.10$, $I^2 = 0\%$)
 - PPI cessation at 6 to 12 months (OR 0.81, 95% CI 0.42 to 1.58, $p = 0.55$, $I^2 = 64\%$)
 - Endoscopic dilation at 6 to 12 months (OR 1.56, 95% CI 0.61 to 3.95, $p = 0.12$, $I^2 = 35\%$)
 - Reoperation at 6 to 12 months (OR 0.54, 95% CI 0.22 to 1.34, $p = 0.18$, $I^2 = 0\%$)
 - Postoperative morbidity ranged from 0% to 3% in the MSA groups and 0% to 7% in the fundoplication groups

Evidence Review: MSA

- Bell et al., 2019
 - Eligible patients had moderate-to-severe regurgitation symptoms while taking once-daily PPI therapy for at least 8 weeks
 - Serious methodological limitations raise concern for selection, performance, and attrition bias
 - Resolution of moderate-to-severe regurgitation at 6 months significantly greater in MSA group compared to PPI group (84% vs. 10%, $p < 0.001$)
 - Patients achieving $> 50\%$ improvement in GERD health-related quality of life score significantly greater in MSA group vs. PPI group (81% vs. 8%, $p < 0.001$)
 - Main adverse effect of MSA was dysphagia in 15 patients (32%)

Evidence Summary: MSA

- There is no evidence that MSA reduces the rate of incident Barrett's esophagus or complications of GERD (i.e., stricture)
- There is very low-certainty evidence that MSA is not statistically significantly better than laparoscopic fundoplication for reducing GERD symptoms or stopping PPI therapy
- There is very low-certainty evidence from 1 small RCT with a high risk of bias that MSA is superior to twice-daily PPI therapy for improving GERD symptoms
- There is very low-certainty evidence that the need for endoscopic dilation or reoperation did not differ significantly between MSA and fundoplication

GRADE Table: MSA

| Outcomes | Estimate of Effect for Outcome/ Confidence in Estimate |
|--|---|
| Incident Barrett's esophagus (Critical outcome) | No data |
| Complications of GERD (e.g., stricture) (Critical outcome) | No data |

GRADE Table: MSA

| Outcomes | Estimate of Effect for Outcome/ Confidence in Estimate |
|--|---|
| GERD symptom scores (Important outcome) | <p>No statistically significant difference in GERD health-related quality of life scores with MSA compared to fundoplication at 6 to 12 months</p> <p>Mean difference -0.48 (95% CI -1.05 to 0.09, $p = 0.10$)</p> <p>●○○○ (<i>Very low confidence, based on 6 observational studies, $n = 1,083$</i>)</p> <p>Significantly more patients reported > 50% improvement in GERD health-related quality of life score with MSA (84%) than PPI (10%) at 6 months ($p < 0.001$)</p> <p>●○○○ (<i>Very low confidence, based on 1 RCT, $n = 152$</i>)</p> |

GRADE Table: MSA

| Outcomes | Estimate of Effect for Outcome/ Confidence in Estimate |
|--|---|
| Change in PPI therapy (Important outcome) | <p>No statistically significant difference in PPI cessation with MSA compared to fundoplication at 6 to 12 months OR 0.81 (95% CI 0.42 to 1.58, p = 0.55)</p> <p>●○○○ (Very low confidence, based on 6 observational studies, n = 1,098)</p> <p>91% of patients undergoing MSA reported PPI cessation at 6 months</p> <p>●○○○ (Very low confidence, based on 1 RCT, n = 50)</p> |

GRADE Table: MSA

| Outcomes | Estimate of Effect for Outcome/ Confidence in Estimate |
|------------------------------|--|
| Harms (Important outcome) | <p>No statistically significant difference in need for endoscopic dilation with MSA compared to fundoplication at 6 to 12 months OR 1.56 (95% CI 0.61 to 3.95, p = 0.12) ●○○○ (Very low confidence, based on 5 observational studies, n = 535)</p> <p>No statistically significant difference in need for reoperation with MSA compared to fundoplication at 6 to 12 months 0.54 (95% CI 0.22 to 1.34, p = 0.18) ●○○○ (Very low confidence, based on 3 observational studies, n = 1,187)</p> <p>32% of patients experienced dysphagia; 5% experienced persistent moderate or severe dysphagia at 6 months ●○○○ (Very low confidence, based on 1 RCT, n = 50)</p> |

Payer Policies: MSA

- Washington State Medicaid Program
 - No Washington Medicaid coverage policy was found for MSA
- Medicare
 - No National Coverage Determinations were found for MSA
 - 1 Local Coverage Determination states that LINX[®] Reflux Management System is not considered reasonable and necessary for the treatment of GERD
- Private payers
 - Aetna, Cigna, Moda, and Regence do not provide coverage for MSA

Guidelines: MSA

- 3 guidelines were identified:
 - American College of Gastroenterology
 - More data are needed before widespread usage of MSA can be recommended
 - National Institute for Health and Care Excellence (NICE)
 - MSA should only be used with special arrangements for clinical governance, consent, and audit or research
 - European Association of Endoscopic Surgery
 - Not enough evidence available to recommend an alternative option to laparoscopic fundoplication for severe GERD

Public Comment

- Public comments on MSA submitted by Johnson & Johnson Medical Devices, manufacturer of LINX[®] Reflux Management System
 - Comment: Additional studies should be considered
 - Response: Standard methodology, including comparative studies and systematic reviews, was used
 - Comment: Additional recommendations by professional organizations and AHRQ should be considered
 - Response: 2017 NICE guidance states that evidence of long-term efficacy is inadequate; AHRQ inclusion in Horizon Scans should not be construed as endorsement; American Society of General Surgeons support statements are not from clinical practice guidelines

Discussion: MSA

Values and Preferences

Most GERD patients with symptomatic control on chronic PPI therapy would prefer to continue medical management, although some would choose surgery to avoid possible long-term harm associated with PPIs.

GERD patients for whom PPI therapy isn't working or is needed twice daily would value surgical intervention if safe and effective. The level of laparoscopic intervention would appear to be similar for MSA and Nissen procedures; therefore, many GERD patients might prefer the laparoscopic Nissen or Toupe procedures as better established.

Discussion: MSA

Resource Allocation

Similar to the considerations for TIF, if lesser degrees of GERD severity are treated with MSA rather than chronic medical therapy, surgical treatment costs for the covered population will rise as utilization increases. The magnitude of offsetting savings in PPI or other medical therapy will be variable. Overall, there would most likely be some increase in resource allocation for GERD management with the addition of MSA coverage.

Balance of Benefits and Harms

Although MSA appears to have similar effectiveness and similar adverse events and complications compared to laparoscopic fundoplication, we have very low confidence in the evidence.

Discussion: MSA

Rationale

Based on observational studies and one poor-quality RCT, the level of evidence is insufficient at present to establish the comparative effectiveness of MSA. Some additional costs would be likely with the addition of MSA coverage, and there are no strong values or preferences that would favor MSA over other available GERD treatment options. Our recommendation for non-coverage is weak because future studies may better establish the benefits of the MSA procedure.

Magnetic sphincter augmentation for treatment of GERD is not recommended for coverage (*weak recommendation*).

Health Evidence Review Commission (HERC)

Coverage Guidance: Newer Interventional Procedures for GERD

DRAFT for VbBS/HERC meeting materials 1/17/2019

HERC Coverage Guidance

Transoral incisionless fundoplication (TIF) is recommended for coverage of GERD treatment only when the following criteria are met (*weak recommendation*):

- 18 years of age or older
- Confirmed diagnosis of esophageal reflux by endoscopy, ambulatory pH, or barium swallow testing
- History of GERD symptoms for one year, occurring at least two to three times per week in the past month
- History of daily proton pump inhibitor therapy for the most recent six months
- Body mass index (BMI) ≤ 35
- Absence of all of the following conditions
 - Hiatal hernia larger than 2 cm
 - Esophagitis with LA grade of C or D
 - Barrett's esophagus greater than 2 cm
 - Achalasia
 - Esophageal ulcer
 - Esophageal motility disorder
 - Altered esophageal anatomy preventing insertion of the device
 - Previous failed anti-reflux surgery or procedure

EsophyX® was the only device identified in the evidence reviewed for this coverage guidance. Other transoral fundoplication devices or systems are not recommended for coverage.

For patients who have recurrent symptoms or fail the initial TIF procedure, repeat TIF is not recommended for coverage (*strong recommendation*).

Magnetic sphincter augmentation for treatment of GERD is not recommended for coverage (*weak recommendation*).

Note: Definitions for strength of recommendation are in Appendix A: *GRADE Table Element Descriptions*.

Rationales for each recommendation appear below in the GRADE table.

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Rationale for development of coverage guidances and multisector intervention reports

Coverage guidances are developed to inform coverage recommendations for public and private health plans in Oregon as plan administrators seek to improve patients' experience of care, population health, and the cost-effectiveness of health care. In the era of public and private sector health system transformation, reaching these goals requires a focus on maximizing the benefits and minimizing the harms and costs of health interventions.

HERC uses the following principles in selecting topics for its reports to guide public and private payers:

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

HERC bases its reports on a review of the best available research applicable to the intervention(s) in question. For coverage guidances, which focus on diagnostic and clinical interventions, evidence is evaluated using an adaptation of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology. For more information on coverage guidance methodology, see Appendix A.

Multisector interventions can be effective ways to prevent, treat, or manage disease at a population level. In some cases, HERC has reviewed evidence and identified effective interventions, but has not made formal coverage recommendations when these policies are implemented in settings other than traditional health care delivery systems because effectiveness could depend on the environment in which the intervention is implemented.

GRADE Table

HERC develops recommendations by using the concepts of the GRADE system. GRADE is a transparent and structured process for developing and presenting evidence and for performing the steps involved in developing recommendations. The table below lists the elements that determine the strength of a recommendation. HERC reviews the evidence and assesses each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Estimates of effect are derived from the evidence presented in this document. Assessments of confidence are from the published systematic reviews and meta-analyses, where available and judged to be reliable.

In some cases, no systematic reviews or meta-analyses encompass the most current literature. In those cases, HERC may describe the additional evidence or alter the assessments of confidence in light of all available information. Such assessments are informed by clinical epidemiologists from the Center for Evidence-based Policy. Unless otherwise noted, statements regarding resource allocation, values and preferences, and other considerations are the assessments of HERC, as informed by the evidence reviewed, public testimony, and subcommittee discussion.

Recommendations for coverage are based on the balance of benefit and harms, resource allocation, values and preferences, and other considerations. See Appendix A for more details about the factors that constitute the GRADE table.

DRAFT

GRADE Table

Should transoral incisionless fundoplication (TIF) be recommended for coverage for GERD?

| Outcomes | Estimate of Effect for Outcome/ <i>Confidence in Estimate</i> | Resource Allocation | Values and Preferences | Other Considerations |
|---|---|---|--|----------------------|
| Incident Barrett's esophagus <i>(Critical outcome)</i> | No data | Professional fees for the TIF procedure are generally lower than the fees for laparoscopic surgical procedures, but when facility and ancillary costs are taken into account, the difference in total procedure costs may not be significant. If lesser degrees of GERD severity are treated with TIF rather than chronic medical therapy, surgical treatment costs for the covered population will | For patients with chronic GERD symptomatology, we would expect values and preferences to be highly variable between medical and surgical treatment options, depending on the severity of symptoms and disease complications. Most patients with symptomatic control on chronic | |
| Complications of GERD (e.g., stricture) <i>(Critical outcome)</i> | No data | | | |
| GERD symptom scores <i>(Important outcome)</i> | Treatment response at 6 months 124/188 (66%) for intervention vs. 32/105 (30%) for control/sham ARD = 36% NNT = 2-3 RR 2.44 (95% CI 1.44 to 1.79, p = 0.02) ●●○○ (Low confidence, based on 4 RCTs, n = 293) | | | |
| Change in PPI therapy <i>(Important outcome)</i> | At 6 months, approximately 70% of patients reported PPI cessation ●●○○ (Low confidence, based on 9 observational studies, n = 439) | | | |

Should transoral incisionless fundoplication (TIF) be recommended for coverage for GERD?

| Outcomes | Estimate of Effect for Outcome/ <i>Confidence in Estimate</i> | Resource Allocation | Values and Preferences | Other Considerations |
|--|---|--|---|----------------------|
| <p>Harms <i>(Important outcome)</i></p> | <p>Overall rate of serious adverse events was 2.4% ●●○○ (Low confidence, based on 12 observational studies and 4 RCTs, n = 781)</p> | <p>rise as TIF utilization increases. The magnitude of offsetting savings in PPI or other medical therapy will vary, depending on the pricing of generic and brand name drugs.</p> | <p>PPI therapy would prefer to continue medical management, although some would choose surgery to avoid possible long-term harm associated with PPIs. GERD patients for whom PPI therapy isn't working or is needed twice daily would value surgical intervention if safe and effective. Many would prefer TIF as a less invasive procedure, but others would prefer the laparoscopic Nissen or Toupe procedures as better established.</p> | |

Should transoral incisionless fundoplication (TIF) be recommended for coverage for GERD?

| Outcomes | Estimate of Effect for Outcome/ <i>Confidence in Estimate</i> | Resource Allocation | Values and Preferences | Other Considerations |
|--|--|---------------------|------------------------|----------------------|
| <p>Balance of benefits and harms: Based on low-certainty evidence, the TIF procedure using the EsophyX® device appears to be effective in improving GERD-related quality of life and reducing or eliminating the need for chronic PPI therapy. There is no evidence that TIF reduces the rate of incident Barrett’s esophagus or complications of GERD (e.g., stricture). Serious adverse effects (including perforation, bleeding, and pneumothorax) do occur with TIF, but the overall 2.4% rate of these events suggests that, on balance, the benefits of TIF outweigh the harms.</p> | | | | |
| <p>Rationale: Although there is no evidence directly comparing TIF with laparoscopic fundoplication procedures, overall the two surgical approaches appear to have similar effectiveness. Coverage of the TIF procedure will not significantly change resource allocation for GERD management, and values and preferences would favor inclusion of TIF coverage, especially as an option for GERD patients whose symptoms are not controlled on chronic medical therapy. Current published evidence supports the safety and efficacy of the EsophyX® device used in this procedure. EsophyX® was the only device included in the systematic reviews and randomized trials that were identified for this coverage guidance. Other TIF devices and systems are not recommended for coverage because there are no comparative data. Our recommendation to cover the TIF procedure is weak because of our low level of confidence in the evidence.</p> | | | | |
| <p>Recommendation: Transoral incisionless fundoplication (TIF) is recommended for coverage for GERD treatment only when the following criteria are met (<i>weak recommendation</i>):</p> <ul style="list-style-type: none"> • 18 years of age or older • Confirmed diagnosis of esophageal reflux by endoscopy, ambulatory pH, or barium swallow testing • History of GERD symptoms for one year, occurring at least two to three times per week in the past month • History of daily proton pump inhibitor therapy for the most recent six months • Body mass index (BMI) ≤ 35 • Absence of all of the following conditions <ul style="list-style-type: none"> ○ Hiatal hernia larger than 2 cm ○ Esophagitis with LA grade of C or D ○ Barrett’s esophagus greater than 2 cm ○ Achalasia ○ Esophageal ulcer ○ Esophageal motility disorder | | | | |

Should transoral incisionless fundoplication (TIF) be recommended for coverage for GERD?

| Outcomes | Estimate of Effect for Outcome/ Confidence in Estimate | Resource Allocation | Values and Preferences | Other Considerations |
|---|---|---------------------|------------------------|----------------------|
| <ul style="list-style-type: none"> ○ Altered esophageal anatomy preventing insertion of the device ○ Previous failed anti-reflux surgery or procedure <p>EsophyX® was the only device identified in the evidence reviewed for this coverage guidance. Other transoral fundoplication devices or systems are not recommended for coverage.</p> <p>For patients who have recurrent symptoms or fail the initial TIF procedure, repeat TIF is not recommended for coverage (<i>strong recommendation</i>).</p> | | | | |

Should magnetic sphincter augmentation (MSA) be recommended for coverage for GERD?

| Outcomes | Estimate of Effect for Outcome/ Confidence in Estimate | Resource Allocation | Values and Preferences | Other Considerations |
|--|--|--|--|----------------------|
| Incident Barrett's esophagus (Critical outcome) | No data | Similar to the considerations for TIF, if lesser degrees of GERD severity are treated with MSA rather than chronic medical therapy, surgical treatment costs for the covered population will rise as utilization increases. The magnitude of | Most GERD patients with symptomatic control on chronic PPI therapy would prefer to continue medical management, although some would choose surgery to avoid possible long-term | |
| Complications of GERD (e.g., stricture) (Critical outcome) | No data | | | |
| GERD symptom scores (Important outcome) | No statistically significant difference in GERD health-related quality of life scores with MSA compared to fundoplication at 6 to 12 months Mean difference -0.48 (95% CI -1.05 to 0.09, p = 0.10) | | | |

Should magnetic sphincter augmentation (MSA) be recommended for coverage for GERD?

| Outcomes | Estimate of Effect for Outcome/ Confidence in Estimate | Resource Allocation | Values and Preferences | Other Considerations |
|---|--|--|--|----------------------|
| | <p>●○○○ (Very low confidence, based on 6 observational studies, n = 1,083)</p> <p>Significantly more patients reported > 50% improvement in GERD health-related quality of life score with MSA (84%) than PPI (10%) at 6 months (p < 0.001)</p> <p>●○○○ (Very low confidence, based on 1 RCT, n = 152)</p> | offsetting savings in PPI or other medical therapy will be variable. Overall, there would most likely be some increase in resource allocation for GERD management with the addition of MSA coverage. | harm associated with PPIs. GERD patients for whom PPI therapy isn't working or is needed twice daily would value surgical intervention if safe and effective. The level of laparoscopic intervention would appear to be similar for MSA and Nissen procedures; therefore, many GERD patients might prefer the laparoscopic Nissen or Toupe procedures as better established. | |
| Change in PPI therapy (Important outcome) | <p>No statistically significant difference in PPI cessation with MSA compared to fundoplication at 6 to 12 months OR 0.81 (95% CI 0.42 to 1.58, p = 0.55)</p> <p>●○○○ (Very low confidence, based on 6 observational studies, n = 1,098)</p> <p>91% of patients undergoing MSA reported PPI cessation at 6 months</p> <p>●○○○ (Very low confidence, based on 1 RCT, n = 50)</p> | | | |
| Harms (Important outcome) | <p>No statistically significant difference in need for endoscopic dilation with MSA compared to fundoplication at 6 to 12 months OR 1.56 (95% CI 0.61 to 3.95, p = 0.12)</p> <p>●○○○ (Very low confidence, based on 5 observational studies, n = 535)</p> <p>No statistically significant difference in need for reoperation with MSA compared to fundoplication at 6 to 12 months</p> | | | |

Should magnetic sphincter augmentation (MSA) be recommended for coverage for GERD?

| Outcomes | Estimate of Effect for Outcome/ <i>Confidence in Estimate</i> | Resource Allocation | Values and Preferences | Other Considerations |
|----------|---|---------------------|------------------------|----------------------|
| | <p>0.54 (95% CI 0.22 to 1.34, p = 0.18)</p> <p>●○○○ (Very low confidence, based on 3 observational studies, n = 1,187)</p> <p>32% of patients experienced dysphagia; 5% experienced persistent moderate or severe dysphagia at 6 months</p> <p>●○○○ (Very low confidence, based on 1 RCT, n = 50)</p> | | | |

Balance of benefits and harms: Although MSA appears to have similar effectiveness and similar adverse events and complications compared to laparoscopic fundoplication, we have very low confidence in the evidence.

Rationale: Based on observational studies and one poor-quality RCT, the level of evidence is insufficient at present to establish the comparative effectiveness of MSA. Some additional costs would be likely with the addition of MSA coverage, and there are no strong values or preferences that would favor MSA over other available GERD treatment options. Our recommendation for non-coverage is weak because future studies may better establish the benefits of the MSA procedure.

Recommendation: Magnetic sphincter augmentation for treatment of GERD is not recommended for coverage (*weak recommendation*).

Note: GRADE table elements are described in Appendix A. A GRADE Evidence Profile is in Appendix B.

Background

Gastroesophageal reflux disease (GERD) is a long-lasting and more serious form of gastroesophageal reflux (or acid reflux). The lower esophageal sphincter becomes weak or relaxes, allowing stomach contents to rise up into the esophagus. Common symptoms of GERD include heartburn, bad breath, nausea, pain in the chest or upper part of the abdomen, painful swallowing, and vomiting. Patients with GERD can sometimes breathe stomach acid into the lungs, provoking asthma, laryngitis, or pneumonia. GERD can also cause Barrett's esophagus, a precursor of esophageal adenocarcinoma (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDKD], 2018).

An estimated 20% of the U.S. population has GERD. Populations at higher risk for GERD include people who are overweight, pregnant women, people who smoke or are exposed to secondhand smoke, and people taking certain medicines (e.g., calcium channel blockers, antihistamines, sedatives, antidepressants, asthma medications, pain medications). GERD is often classified by the frequency and severity of symptoms. Procedures to test for GERD include upper gastrointestinal endoscopy and biopsy, x-rays of the upper gastrointestinal area, and esophageal pH and impedance monitoring (NIDDKD, 2018).

Lifestyle changes may improve or eliminate GERD, such as not overeating, not eating two to three hours before sleeping, quitting smoking and avoiding secondhand smoke, wearing loose-fitting clothing around the abdomen, and sleeping on a bed that is on a slight angle. Medicines (both prescription and nonprescription) to treat GERD include antacids, histamine 2 receptor antagonists, proton pump inhibitors (PPI), and prokinetic agents (NIDDKD, 2018).

The most common surgery for GERD is laparoscopic fundoplication, in which the top of the stomach is sewed around the esophagus to add pressure to the lower end of the esophagus and reduce reflux. Laparoscopic fundoplication is performed under general anesthesia, and most patients return to usual activities in two to three weeks (NIDDKD, 2018).

The focus of this coverage guidance is two additional treatments for GERD: transoral incisionless fundoplication (TIF) and magnetic sphincter augmentation (MSA).

Indications

Indications for TIF include intractable GERD symptoms, no or mild esophagitis with hiatal hernia < 2 cm, and abnormal acid reflux (Richter et al., 2018).

MSA is performed using the LINX Reflux Management System. This device was approved by the U.S. Food and Drug Administration (FDA) in 2012 and is indicated for patients diagnosed with GERD as defined by abnormal pH testing, and who continue to have chronic GERD symptoms despite maximum therapy for the treatment of reflux (FDA, 2012).

Technology Description

TIF is a minimally invasive, endoscopic technique that restores the valve at the gastroesophageal junction via endoluminal fundoplication using EsophyX (Huang et al., 2017). The EsophyX device is a fastener delivery system designed to reconstruct the gastroesophageal valve and help restore its function as a reflux barrier. Approximately 20 fasteners are implanted during the procedure to create

fusion of the esophageal and fundus tissues and form the valve (EndoGastric Solutions, 2016). The first iteration of TIF (sometimes called TIF 1.0) creates the fundoplication wrap around the gastroesophageal junction; the later version of the procedure (TIF 2.0) creates the wrap around the intraabdominal portion of the esophagus.

The LINX Reflux Management System is a small, flexible ring of interlinked titanium beads with magnetic cores that is placed around the esophagus just above the stomach during a laparoscopic procedure. A sizing tool is used to determine the appropriate size LINX System, and the device is positioned using sutures. The magnetic attraction between the beads helps the lower esophageal sphincter resist opening because of gastric pressures. Swallowing temporarily breaks the magnetic bonds, allowing food and liquid to pass normally into the stomach (Torax Medical, 2018).

Evidence Review

Huang et al., 2017

This is a good-quality systematic review and meta-analysis of prospective studies of TIF. The primary outcome measure for the meta-analysis was treatment response at six months defined as improvement of at least 50% in the GERD health-related quality of life score, or remission of heartburn and regurgitation, or complete cessation of PPI therapy; these outcomes were considered hierarchically in the order described (i.e., cessation of PPI therapy only contributed to the outcome if the other two outcomes were not reported). The authors identified five randomized controlled trials (total n = 343) published in 2014 and 2015, all of which used the TIF 2.0 procedure. Two of the RCTs compared TIF to a sham procedure, and three trials compared TIF to PPI therapy. The included trials were mainly low to moderate risk of bias, although one trial was deemed to be at high risk of bias due to concerns with blinding and attrition. Three of the five studies were sponsored by the manufacturer of the EsophyX TIF system. The authors also identified 13 prospective observational studies, but these were not included in the primary meta-analyses. In general, studies excluded patients with large hiatal hernias or BMI greater than 30 or 35 kg/m².

For the primary outcome of treatment response at six months, four studies with 293 patients contributed to the meta-analysis. Overall, in the intention-to-treat analysis, treatment response occurred in 124 of the 188 patients randomized to TIF (66%) compared to 32 of 105 patients randomized to the control group (30%) (RR 2.44, 95% CI 1.44 to 4.79, p = 0.02, I² = 70%). Data from the prospective observational studies were not meta-analyzed, but did allow for an assessment of the durability of treatment effects beyond six months. Based on these studies, the treatment response to TIF appears to be sustained through 36 months but then begins to decline, although estimates beyond 36 months are based on very small numbers of patients. Similarly, the analysis of PPI use in prospective observational studies shows a sustained effect for PPI cessation between 12 and 36 months of follow-up (rate of approximately 60%), but the rate of PPI cessation beyond 36 months falls to 30-50% (again based on a very small number of observations).

Five-year follow-up from one of the included RCTs was separately reported (Trad et al., 2018). In this study, all control group patients crossed over to TIF after six months (total n = 63, of whom 44 had available data for follow-up at five years). At five years, there was sustained improvement in GERD health-related quality of life score compared to baseline (22.2 at baseline to 6.8 at five years, p < 0.01), although the rate of PPI use steadily increased from 17% at one year to 34% at five years.

In a total of 16 studies (four RCTs and 12 observational studies), there were 19 serious adverse events among 781 patients who received the TIF procedure (2.4%). These events included seven perforations, five episodes of bleeding, four pneumothoraces, and one death (reported 20 months after the TIF procedure). In the five-year follow-up reported by Trad et al. (2018), there were no serious adverse events, but three patients (5%) did require reoperation.

Richter et al., 2018

Because there are no RCTs directly comparing TIF with laparoscopic Nissen fundoplication (LNF), Richter et al. undertook a network meta-analysis (NMA), which allows for indirect comparisons. The PPI node allowed for an indirect comparison of TIF and LNF (120 patients were included in the TIF vs. PPI trials, and 835 patients were included in the LNF vs. PPI trials). For the NMA outcome of improved GERD health-related quality of life, TIF was found to have the greatest probability of being the best treatment (surface under the cumulative ranking curve of 0.92) followed by LNF (surface under the cumulative ranking curve of 0.66), although in the pairwise comparison the difference between the two procedures was not statistically significant (OR 2.08, 95% CI 0.71 to 6.09) and the quality of evidence was judged to be very low. The authors of this study also queried the MAUDE database for reports on the TIF procedure and found 50 cases of device malfunction and 75 cases of injury including 36 perforations, 10 gastrointestinal bleeds, 8 esophageal lacerations, 8 pleural effusions, and 6 mediastinal abscesses (out of an unknown denominator of total TIF procedures).

Aiolfi et al., 2018

This is a fair-quality systematic review and meta-analysis of seven observational studies comparing MSA with laparoscopic fundoplication (Nissen or Toupe techniques). The review is mainly limited by incomplete reporting of the quality ratings of the included studies. One study was a prospective cohort and the remaining six studies were retrospective cohorts. The included studies were published between 2014 and 2017 and involved 1,211 patients in total; 686 patients (56%) were treated with MSA and 524 (44%) underwent laparoscopic fundoplication. The mean age of patients ranged from approximately 40 to 55 years old, the mean BMI ranged from 24 to 30 kg/m², and the mean hiatal hernia size ranged from 1 to 2 cm. Six studies with 1,083 patients contributed to the random effects meta-analysis of the pooled mean difference in GERD health-related quality of life score at six to 12 months, which found a non-statistically significant difference of -0.48 (95% CI -1.05 to 0.09, $p = 0.10$, $I^2 = 0\%$). Six studies with 1,098 patients contributed to the random effects meta-analysis of the pooled odds ratio of PPI cessation at six to 12 months, which found a non-statistically significant difference of 0.81 (95% CI 0.42 to 1.58, $p = 0.55$, $I^2 = 64\%$). Five studies with 535 patients contributed to the random effects meta-analysis of the pooled odds ratio of endoscopic dilation at six to 12 months, which found a non-statistically significant difference of 1.56 (95% CI 0.61 to 3.95, $p = 0.12$, $I^2 = 35\%$). Three studies with 1,187 patients contributed to the random effects meta-analysis of the pooled odds ratio of reoperation at six to 12 months, which found a non-statistically significant difference of 0.54 (95% CI 0.22 to 1.34, $p = 0.18$, $I^2 = 0\%$). In terms of harms, the authors observed that overall postoperative morbidity ranged from 0% to 3% in the MSA groups and 0% to 7% in the fundoplication groups. The ability to vomit or belch was better preserved in the MSA groups compared to the fundoplication groups.

Bell et al., 2019

This is a poor-quality randomized controlled trial of MSA compared to twice-daily PPI therapy for patients with persistent GERD despite once-daily PPI. Eligible patients were over age 21 and had moderate-to-severe regurgitation symptoms while taking once-daily PPI therapy for at least eight weeks. Patients who were already on twice-daily PPI, had hiatal hernias larger than 3 cm, BMI > 35 kg/m², or who had grade C or D esophagitis or Barrett's esophagus or esophageal strictures were excluded. Patients were mainly recruited from surgical clinics. Overall, 152 patients were enrolled and randomized in 2:1 fashion to twice-daily PPI or MSA after a one week washout period off their once-daily PPI treatment. In the intention-to-treat analysis, the primary endpoint of resolution of moderate-to-severe regurgitation at six months was achieved in 84% of the MSA group and 10% of the PPI group ($p < 0.001$). Similarly, the percentage of patients achieving > 50% improvement in the GERD health-related quality of life score was 81% in the MSA group and 8% in the PPI group ($p < 0.001$). In the MSA group, 91% of patients had stopped using PPI at six months. The main adverse effect of MSA was dysphagia, which occurred in 15 patients (32%). This dysphagia was reported as minimal or resolved for 13 patients by six months, but was persistent and moderate or severe in two patients at six months.

There were several methodological limitations to this trial. The manuscript does not describe methods for random sequence generation or allocation concealment. Study participants were not blinded to treatment group, which increases the risk of performance bias for subjectively reported outcomes. This concern about a placebo effect is heightened by the recruitment of participants from surgical clinics. Although the overall rate of attrition at six months was modest, it was different in the MSA group (0%) and the PPI group (14%). There was no statement in the manuscript regarding trial funding, sponsorship, or conflicts of interest.

Evidence Summary

There is no evidence that either TIF or MSA reduce the rate of incident Barrett's esophagus or complications of GERD (e.g., stricture). There is low-certainty evidence that TIF improved treatment response compared with sham procedures and/or PPI, although the durability of that improvement beyond 36 months is less certain. Many patients who underwent TIF were able to stop PPI treatment. The overall rate of adverse effects with TIF is approximately 2.5% in the studies. There are no direct randomized comparisons of TIF and laparoscopic fundoplication procedures, but a network meta-analysis suggested that there was no statistically significant difference between the two procedures in the odds of improving GERD health-related quality of life.

There is very low-certainty evidence that MSA is not statistically significantly better than laparoscopic fundoplication for reducing GERD symptoms or stopping PPI therapy. There is very low-certainty evidence from one small RCT with a high risk of bias that MSA is superior to twice-daily PPI therapy for improving GERD symptoms. There is very low-certainty evidence that the need for endoscopic dilation or reoperation did not differ significantly between MSA and fundoplication; the rate of dysphagia in the MSA group of the sole randomized trial was 32%, although only 5% had persistent moderate-to-severe dysphagia at six months.

Policy Landscape

Payer Coverage Policies

Medicaid

No coverage policies were found for Washington Medicaid for either TIF or MSA.

Medicare

No Medicare National Coverage Determinations were found for TIF or MSA, and two Local Coverage Determinations (LCD) were found for these procedures. Two LCDs provide coverage for TIF. [L34659](#) (revision effective 1/1/2018) provides coverage of TIF for treatment of patients in whom PPI therapy fails. The procedure must be done by a well-trained surgeon, and the patient must meet these conditions:

- Symptomatic chronic gastroesophageal reflux (defined as > 6 months of symptoms)
- Symptoms must not be completely responsive to PPI as judged by GERD HRQL scores of ≤ 12 while on PPI and ≥ 20 when off for 14 days (or difference ≥ 10 of the scores between off and on therapy)
- Hiatal hernia ≤ 2 cm, if present

Coverage is not extended for patients who have recurrent symptoms or fail this procedure, and repeat TIF is considered investigational. This LCD does not mention MSA.

The other LCD, [L35080](#) (revision effective 12/1/2017), provides coverage for TIF, except for patients:

- Who have recurrent symptoms or other evidence of failure following a prior TIF
- In which a staged procedure is being done (i.e., laparoscopic esophageal or paraesophageal diaphragmatic hernia/opening closure followed by a TIF endoscopically)
- Who have a preoperative hiatal hernia > 2 cm
- With BMI > 35, esophagitis LA grade > B, Barrett's esophagus > 2 cm, and presence of achalasia or esophageal ulcer or has not been on an appropriate trial of PPI

This LCD states that LINX® Reflux Management System, a MSA device, is not considered reasonable and necessary for the treatment of GERD.

A third LCD, [L33296](#) (revision effective 1/25/2018), states that transesophageal endoscopic procedures (e.g., TIF) for the treatment of GERD are not covered.

Private Payers

Coverage policies were searched for four private payers: Aetna, Cigna, Moda, and Regence. None of these private payers covered MSA, and only Moda covered TIF. The Moda policy on [endoscopic procedures for GERD](#) (effective 7/1/2018) provides coverage for TIF when all these conditions are met:

- a. 18 years of age or older
- b. Confirmed diagnosis of esophageal reflux by endoscopy, ambulatory pH, or barium swallow testing
- c. History of GERD symptoms for one year occurring two to three times per week
- d. GERD patients with body mass index (BMI) ≤ 35
- e. History of daily PPI therapy for greater than six months

- f. Absence of all of the following conditions:
 - i. Absence of a hiatal hernia or one that is 2 cm or less
 - ii. No esophagitis LA grade C or D
 - iii. Barrett's esophagus, or if present it is 2 cm or less
 - iv. Achalasia
 - v. Esophageal ulcer
 - vi. Esophageal motility disorder
 - vii. Altered esophageal anatomy preventing insertion of the device
 - viii. No [sic] previous failed anti-reflux surgery/procedure

This Moda policy considers MSA to be investigational.

The Aetna policy on [GERD treatment devices](#) (last review 5/24/18) does not cover StomaphyX or EsophyX (TIF devices) or LINX Reflux Management System (a sphincter augmentation device). The Cigna policy on [endoscopic anti-reflux procedures](#) (effective 3/15/18) does not provide coverage for TIF or injection/implantation of biocompatible material, such as the LINX Reflux Management System. The Regence policy on [transesophageal endoscopic therapies for GERD](#) (effective 3/1/2018) does not provide coverage for TIF, and the Regence policy on [MSA](#) (effective 3/1/2018) does not provide coverage for that procedure.

Recommendations from Others

The search for clinical practice guidelines found guidelines from three organizations: American College of Gastroenterology, National Institute for Health and Care Excellence (NICE), and European Association of Endoscopic Surgery. All of these guidelines generally recommended against the use of TIF or MSA.

The American College of Gastroenterology guidelines on diagnosis and management of GERD (Katz et al., 2013) states that TIF cannot be recommended as an alternative to medical or traditional surgical therapy. These guidelines discuss the LINX Reflux System and state that more data are needed before widespread usage of LINX can be recommended.

The NICE guidelines on GERD in adults do not mention TIF or MSA (NICE, 2014). A more recent interventional procedures guidance from NICE concludes:

There are no major safety concerns about laparoscopic insertion of a magnetic titanium ring for [GERD]. There is limited evidence of short-term efficacy, but evidence of long-term efficacy is inadequate in quality and quantity. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research (NICE, 2017, p.2).

The European Association of Endoscopic Surgery guidelines on GERD (Fuchs et al., 2014) conclude that there is not enough evidence available to recommend an alternative option to laparoscopic fundoplication for severe GERD.

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Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

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Appendix A. GRADE Table Element Descriptions

| Element | Description |
|-------------------------------|---|
| Balance of benefits and harms | The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. An estimate that is not statistically significant or has a confidence interval crossing a predetermined clinical decision threshold will be downgraded. |
| Quality of evidence | The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted |
| Resource allocation | The higher the costs of an intervention—that is, the greater the resources consumed in the absence of likely cost offsets—the lower the likelihood that a strong recommendation is warranted |
| Values and preferences | The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted |
| Other considerations | Other considerations include issues about the implementation and operationalization of the technology or intervention in health systems and practices within Oregon. |

Strong recommendation

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

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

Weak recommendation

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

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

Confidence in estimate rating across studies for the intervention/outcome

Assessment of confidence in estimate includes factors such as risk of bias, precision, directness, consistency and publication bias.

High: The subcommittee is very confident that the true effect lies close to that of the estimate of the effect. Typical sets of studies are RCTs with few or no limitations and the estimate of effect is likely stable.

Moderate: The subcommittee is moderately confident in the estimate of effect: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.

Low: The subcommittee's confidence in the estimate of effect is limited: The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

Very low: The subcommittee has very little confidence in the estimate of effect: The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

DRAFT

Appendix B. GRADE Evidence Profile

| Quality Assessment (Confidence in Estimate of Effect) | | | | | | | |
|---|-----------------|--------------|---------------|--------------|-------------|---------------|-------------|
| Transoral Incisionless Fundoplication | | | | | | | |
| No. of Studies | Study Design(s) | Risk of Bias | Inconsistency | Indirectness | Imprecision | Other Factors | Quality |
| Incident Barrett's esophagus | | | | | | | |
| 0 | | | | | | | No data |
| Complications of GERD | | | | | | | |
| 0 | | | | | | | No data |
| GERD symptom scores (Treatment response) | | | | | | | |
| 4 | RCTs | Moderate | Serious | Not serious | Not serious | | Low ●●○○ |
| Change in PPI therapy | | | | | | | |
| 9 | Observational | Low | Not serious | Not serious | Not serious | | Low ●●○○ |
| Harms | | | | | | | |
| 12 | Mixed | Low | Not serious | Not serious | Not serious | | Low ●●○○ |

| Quality Assessment (Confidence in Estimate of Effect) | | | | | | | |
|--|-----------------|--------------|---------------|--------------|-------------|---------------|------------------|
| Magnetic Sphincter Augmentation Compared to Fundoplication | | | | | | | |
| No. of Studies | Study Design(s) | Risk of Bias | Inconsistency | Indirectness | Imprecision | Other Factors | Quality |
| Incident Barrett's esophagus | | | | | | | |
| 0 | | | | | | | No data |
| Complications of GERD | | | | | | | |
| 0 | | | | | | | No data |
| GERD symptom scores | | | | | | | |
| 6 | Observational | Moderate | Not serious | Not serious | Serious | | Very Low ●○○○ |
| Change in PPI therapy | | | | | | | |
| 6 | Observational | Moderate | Not serious | Not serious | Serious | | Very Low ●○○○ |
| Harms | | | | | | | |
| Endoscopic dilation 5 | Observational | Moderate | Not serious | Not serious | Serious | | Very Low ●○○○ |
| Re-operation 3 | | | | | | | |

| Quality Assessment (Confidence in Estimate of Effect) | | | | | | | |
|---|-----------------|--------------|---------------|--------------|--------------|---------------|------------------|
| Magnetic Sphincter Augmentation Compared to PPI | | | | | | | |
| No. of Studies | Study Design(s) | Risk of Bias | Inconsistency | Indirectness | Imprecision | Other Factors | Quality |
| Incident Barrett's esophagus | | | | | | | |
| 0 | | | | | | | No data |
| Complications of GERD | | | | | | | |
| 0 | | | | | | | No data |
| GERD symptom scores | | | | | | | |
| 1 | RCT | High | N/A | Not serious | Not reported | Sparse data | Very Low ●○○○ |
| Change in PPI therapy | | | | | | | |
| 1 | RCT | High | N/A | Not serious | Not reported | Sparse data | Very Low ●○○○ |
| Harms | | | | | | | |
| 1 | RCT | High | N/A | Not serious | Not reported | Sparse data | Very Low ●○○○ |

Appendix C. Methods

Scope Statement

Populations

Adults with gastroesophageal reflux disease (GERD)

Population scoping notes: None

Interventions

Laparoscopic magnetic ring procedure for augmentation of the lower esophageal sphincter; transoral incisionless fundoplication

Intervention exclusions: None

Comparators

Medical management, Nissen fundoplication, interventions compared to each other, sham interventions

Outcomes

Critical: Incident Barrett's esophagus, complications of GERD (e.g., stricture)

Important: GERD symptom scores, change in proton pump inhibitor (PPI) therapy, harms (e.g., repeat interventions)

Considered but not selected for the GRADE table: None

Key Questions

KQ1: What is the comparative effectiveness of magnetic sphincter augmentation of the lower esophageal sphincter and transoral incisionless fundoplication in the treatment of GERD?

KQ2: How does the effectiveness of magnetic sphincter augmentation of the lower esophageal sphincter and transoral incisionless fundoplication in the treatment vary by:

- a. Patient characteristics (e.g., age, gender, weight, tobacco use)
- b. Comorbid conditions
- c. Duration of symptoms
- d. Response to prior treatments
- e. Procedural technique

KQ3: What are the harms of magnetic sphincter augmentation of the lower esophageal sphincter and transoral incisionless fundoplication in the treatment of GERD?

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, and technology assessments that meet the criteria for the scope described above. Searches of core sources were limited to citations published after 2013.

The following core sources were searched:

- Agency for Healthcare Research and Quality (AHRQ)
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Online Library)
- Institute for Clinical and Economic Review (ICER)
- Medicaid Evidence-based Decisions Project (MED)
- National Institute for Health and Care Excellence (NICE)
- Tufts Cost-effectiveness Analysis Registry
- Veterans Administration Evidence-based Synthesis Program (ESP)
- Washington State Health Technology Assessment Program

A MEDLINE® search was also conducted to identify systematic reviews, meta-analyses, and technology assessments, using the search terms gastroesophageal reflux disease (GERD) and magnetic or transoral fundoplication. The search was limited to publications in English published since 2012. In addition, a MEDLINE® search was conducted for randomized controlled trials published after the search dates of the most recent systematic review selected for each indication.

Searches for clinical practice guidelines were limited to those published since 2013. A search for relevant clinical practice guidelines was also conducted using MEDLINE® and the following sources:

- Australian Government National Health and Medical Research Council (NHMRC)
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Centers for Disease Control and Prevention (CDC), Community Preventive Services
- National Guidelines Clearinghouse
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Preventive Services Task Force (USPSTF)
- Veterans Administration/Department of Defense (VA/DoD) Clinical Practice Guidelines

Inclusion/Exclusion Criteria

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

Appendix D. Applicable Codes

| CODES | DESCRIPTION |
|------------------|--|
| CPT Codes | |
| 43210 | Esophagogastroduodenoscopy, flexible, transoral; with esophagogastric fundoplasty, partial or complete, includes duodenoscopy when performed |
| 43284 | Laparoscopy, surgical, esophageal sphincter augmentation procedure, placement of sphincter augmentation device (ie, magnetic band), including cruroplasty when performed |
| 43285 | Removal of esophageal sphincter augmentation device |

Note: Inclusion on this list does not guarantee coverage.

DRAFT

Question: How should the draft Coverage Guidance **Newer Interventional Procedures for GERD** be applied to the Prioritized List?

Question source: HERC Staff, HTAS

Issue:

The HTAS approved the following draft “box language”:

Transoral incisionless fundoplication (TIF) is recommended for coverage of GERD treatment only when the following criteria are met (*weak recommendation*):

- 18 years of age or older
- Confirmed diagnosis of esophageal reflux by endoscopy, ambulatory pH, or barium swallow testing
- History of GERD symptoms for one year, occurring at least two to three times per week in the past month
- History of daily proton pump inhibitor therapy for the most recent six months
- Body mass index (BMI) ≤ 35
- Absence of all of the following conditions
 - Hiatal hernia larger than 2 cm
 - Esophagitis with LA grade of C or D
 - Barrett’s esophagus greater than 2 cm
 - Achalasia
 - Esophageal ulcer
 - Esophageal motility disorder
 - Altered esophageal anatomy preventing insertion of the device
 - Previous failed anti-reflux surgery or procedure

EsophyX® was the only device identified in the evidence reviewed for this coverage guidance. Other transoral fundoplication devices or systems are not recommended for coverage.

For patients who have recurrent symptoms or fail the initial TIF procedure, repeat TIF is not recommended for coverage (*strong recommendation*).

Magnetic sphincter augmentation for treatment of GERD is not recommended for coverage (*weak recommendation*).

Rationale for Recommendations:

Transoral incisionless fundoplication (TIF) is a minimally invasive, endoscopic technique that restores the valve at the gastroesophageal junction via endoluminal fundoplication using the EsophyX device. Magnetic sphincter augmentation (MSA) is performed using the LINX Reflux Management System, which is a small, flexible ring of interlinked titanium beads with magnetic cores that is placed around the esophagus just above the stomach during a laparoscopic procedure.

Based on low-certainty evidence, the TIF procedure using the EsophyX® device appears to be effective in improving GERD-related quality of life and reducing or eliminating the need for chronic PPI therapy. Serious adverse events (including perforation, bleeding, and pneumothorax) do occur with TIF, but the

Coverage Guidance: Newer Interventional Procedures for GERD

overall 2.4% rate of these events suggests that, on balance, the benefits of TIF outweigh the harms. Although there is no evidence directly comparing TIF with laparoscopic fundoplication procedures, overall the two surgical approaches appear to have similar effectiveness. Values and preferences would favor inclusion of TIF coverage, especially as an option for GERD patients whose symptoms are not controlled on chronic medical therapy.

Current published evidence supports the safety and efficacy of the EsophyX® device used in this procedure. EsophyX® was the only device included in the systematic reviews and randomized trials that were identified for this coverage guidance.

Although the MSA procedure appears to have similar effectiveness and similar adverse events and complications compared to laparoscopic fundoplication, we have very low confidence in the evidence. Based on observational studies and one poor-quality RCT, the level of evidence is insufficient at present to establish the comparative effectiveness of MSA. Some additional costs would be likely with the addition of MSA coverage, and there are no strong values or preferences that would favor MSA over other available GERD treatment options.

Current Prioritized List Status: Codes

On the January 1, 2019 Prioritized List, transoral incisionless fundoplication (CPT 43210) is placed on lines 56 and 380. Magnetic sphincter augmentation (CPT 43284) does not appear on the List.

| CPT Codes | |
|-----------|--|
| 43210 | Esophagogastroduodenoscopy, flexible, transoral; with esophagogastric fundoplasty, partial or complete, includes duodenoscopy when performed |
| 43284 | Laparoscopy, surgical, esophageal sphincter augmentation procedure, placement of sphincter augmentation device (ie, magnetic band), including cruroplasty when performed |

Line: 56

Condition: ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE

Treatment: MEDICAL AND SURGICAL TREATMENT

Line: 380

Condition: ESOPHAGITIS; GERD

Treatment: SHORT-TERM MEDICAL THERAPY; SURGICAL TREATMENT

Current Prioritized List Guideline:

There are no current Guideline Notes related to transoral incisionless fundoplication or magnetic sphincter augmentation.

HERC Staff Recommendations:

- 1) Remove CPT 43210 (transoral incisionless fundoplication) from line 56 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE
 - a. No appropriate GERD type diagnoses on this line
 - b. Leave only on line 380 ESOPHAGITIS; GERD
- 2) Add a new Guideline Note to line 380, as follows:

GUIDELINE NOTE XXX, TRANSORAL INCISIONLESS FUNDOPLICATION FOR TREATMENT OF GERD

Line 380

Transoral incisionless fundoplication (TIF), CPT 43210, utilizing the EsophyX device only, is included on Line 380 for surgical treatment of GERD only when the patient meets ALL the following criteria:

- 1) 18 years of age or older; AND
- 2) Confirmed diagnosis of esophageal reflux by endoscopy, ambulatory pH, or barium swallow testing; AND
- 3) History of GERD symptoms for one year, occurring at least two to three times per week in the past month; AND
- 4) History of daily proton pump inhibitor therapy for the most recent six months; AND
- 5) Body mass index (BMI) \leq 35, AND
- 6) Absence of ALL of the following conditions
 - a. Hiatal hernia larger than 2 cm
 - b. Esophagitis with LA grade of C or D
 - c. Barrett's esophagus greater than 2 cm
 - d. Achalasia
 - e. Esophageal ulcer
 - f. Esophageal motility disorder
 - g. Altered esophageal anatomy preventing insertion of the device
 - h. Previous failed anti-reflux surgery or procedure

Repeat TIF is not included on Line 380, for patients who have recurrent symptoms or fail the initial TIF procedure.

The development of this guideline note was informed by a HERC coverage guidance. See <http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Evidence-based-Reports.aspx>.

- 3) Add CPT 43284 (magnetic sphincter augmentation) to Line 660, and add an entry to Guideline Note 173 as shown below:

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 660

The following Interventions are prioritized on Line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Coverage Guidance: Newer Interventional Procedures for GERD

| Procedure Code | Intervention Description | Rationale | Last Review |
|-----------------------|--|--|-----------------------------------|
| 43284 | Laparoscopy, surgical, placement of esophageal sphincter augmentation device (ie, magnetic band) | Insufficient evidence of effectiveness | January 2019 Coverage Guidance |

HERC Coverage Guidance: Newer Interventional Procedures for GERD Disposition of Public Comments

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Commenters

| Identification | Stakeholder |
|----------------|--|
| A | Craig Gonzales, RN, MBA, Director, Healthcare Economics, EndoGastric Solutions, Inc. <i>[Submitted October 26, 2018]</i> |
| B | Sudip K. Ghosh, PhD, Director, Health Economics & Market Access, Johnson & Johnson Medical Devices <i>[Submitted October 31, 2018]</i> |

Public Comments

| ID/# | Comment | Disposition |
|------|---|--|
| A1 | <p>On behalf of EndoGastric Solutions (EGS), I am filing the following comments to the draft Coverage Guidance: Newer Interventional Procedures for GERD. EGS is the manufacturer of the EsophyX transoral incisionless fundoplication (TIF) medical device. Since 2005, EGS has marketed the EsophyX TIF surgical implant device for patients with chronic gastroesophageal reflux disease (GERD). All Medicare Administrative Contractors cover the transoral incisionless fundoplication implant procedure for symptomatic beneficiaries who have failed to respond to conservative lifestyle and pharmacologic measures.</p> <p>We understand that Health Evidence Review Committee’s (HERC) purpose is to review clinical literature to prioritize health spending in the Oregon Health Plan (OHP) and to promote evidence-based medical practice statewide through comparative effectiveness reports. EGS supports these goals, and we want to work with HERC to ensure that these goals are met while protecting beneficiaries’ access to innovative new technologies. To that end, we applaud HERC’s draft decision to recommend TIF for treatment of GERD.</p> | <p><i>Thank you for your comments.</i></p> |

HERC Coverage Guidance: Newer Interventional Procedures for GERD Disposition of Public Comments

| ID/# | Comment | Disposition |
|------|--|--|
| | <p>To ensure that the HERC continues to provide OHP with timely, clinically significant analysis, EGS asks HERC to take the following actions:</p> <p>I. HERC should modify the indications and contra-indications in the Coverage Guidance.</p> <p>II. HERC should specify which device is allowed to perform the procedure under the Coverage Guidance.</p> <p>The above issues will be discussed in detail in the following comments.</p> | |
| A2 | <p>I. HERC should modify the indications and contra-indications in the Coverage Guidance.</p> <p>EGS urges HERC to modify the coverage guidance criteria to match that in the instructions for use (IFU) for the device as approved by the FDA. Suggested language is below:</p> <p>INDICATIONS</p> <p>The EndoGastric Solutions EsophyX Z+ Fastener Delivery Device with SerosaFuse® Fastener and accessories is indicated for use in transoral tissue approximation, full thickness plication and ligation in the GI tract and is indicated for the treatment of symptomatic chronic gastroesophageal reflux disease in patients who require and respond to pharmacological therapy. It is also indicated to narrow the gastroesophageal junction and reduce hiatal hernia ≤ 2cm in size in patients with symptomatic chronic gastroesophageal reflux disease. Patients with hiatal hernias larger than 2cm may be included, when a laparoscopic hiatal hernia repair reduces the hernia to 2cm or less.</p> <p>CONTRAINDICATIONS</p> <p>Patients with bleeding disorders, strictures, severe esophagitis, esophageal diverticulae, obstructions, paraesophageal hernia, limited neck mobility, osteophytes of the spine, esophageal varices, esophageal infections or fungal disease, esophageal stenosis and any kind of normal or abnormal esophageal anatomy which would not permit insertion of a device of this size, chronic cough, BMI > 35 or hiatal hernia > 2cm.</p> | <p><i>The subcommittee based its recommendations for indications and contraindications on the published literature as well as the policies of other insurers. The question of whether laparoscopic hiatal hernia repair should be undertaken to permit the use of endoscopic fundoplication is beyond the scope of this coverage guidance, but adding a surgical procedure before endoscopic fundoplication would alter the balance of benefits and harms.</i></p> |
| A3 | <p>II. HERC should specify which device is allowed under the Coverage Guidance.</p> <p>Aside from EndoGastric Solutions' EsophyX Device, the MUSE system from Medigus Ltd. may also be used to perform a variation of the TIF procedure. There are very few published clinical studies on the MUSE system. In fact, there are no published RCTs on the MUSE system. None of the three TIF-focused papers in the draft</p> | <p><i>EsophyX® was the only device that was included in the systematic reviews and randomized trials that were</i></p> |

HERC Coverage Guidance: Newer Interventional Procedures for GERD Disposition of Public Comments

| ID/# | Comment | Disposition |
|------|--|---|
| | <p>Coverage Guidance studied the MUSE system. These papers only studied the TIF procedure performed with the EsophyX device.</p> <p>We suggest that HERC specify which device is allowable under the Coverage Guidance to prevent the inadvertent use of the untested MUSE system. The guidance in Palmetto’s local coverage determination (LCD) provides a suitable template. Suggested language is below:</p> <p>D. Covered Transesophageal Endoscopic Procedure for the Treatment of GERD</p> <p>Transoral incisionless fundoplication (TIF) is a transesophageal endoscopic procedure for the treatment of GERD that is covered under this Local Coverage Determination (LCD). Current published peer reviewed literature supports the safety and efficacy of the EsophyX® device used in this procedure (CPT® Code 43210).</p> <p>EsophyX® is a device used in a transoral incisionless fundoplication (TIF®) procedure to repair the natural anti-reflux barrier and is also indicated to narrow the gastroesophageal junction and reduce hiatal hernia = 2cm in size. EsophyX® includes SerosaFuse® Fasteners and consists of a flexible fastener delivery system comprised of three elements: a stylet, a pusher rod, and a delivery tube. The EsophyX® procedure is designed for use in transoral tissue approximation, full thickness serosa to serosa plications and to construct valves in the gastrointestinal tract which are used. The procedure is performed with the patient under general anesthesia.</p> | <p><i>identified for this coverage guidance.</i></p> <p><i>We have revised the draft recommendation to specify that EsophyX® is the only device identified in the evidence reviewed for this coverage guidance.</i></p> |
| A4 | <p>Conclusion</p> <p>EGS appreciates this opportunity to comment on the HERC Coverage Guidance. We urge HERC to consider our recommendations carefully and make the changes necessary to ensure that Oregon patients have access to state-of-the-art care. As always, EGS looks forward to working with the state in the future to improve access to the best and innovative technologies that our company has to offer.</p> <p>The IFU [indications for use] and LCD referenced are attached to this comment.</p> | <p><i>Thank you for your comments.</i></p> |
| B1 | <p>This communication will serve as a request for reconsideration of the decision noted in the draft coverage guidance for Newer Interventional Procedures for GERD. The decision applies to Magnetic Sphincter Augmentation (MSA) that is associated with the following two procedures:</p> | <p><i>Thank you for your comments.</i></p> <p><i>We believe our search and the included studies in the CG capture all of the available</i></p> |

HERC Coverage Guidance: Newer Interventional Procedures for GERD Disposition of Public Comments

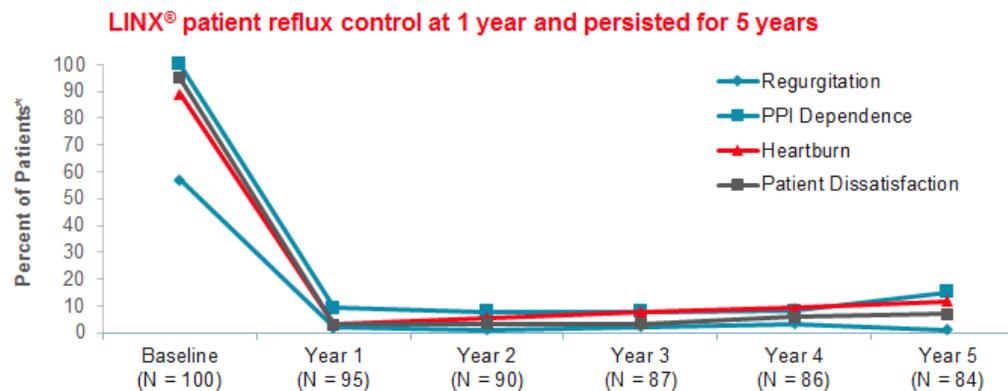
| ID/# | Comment | Disposition |
|------|--|---|
| | <p>43284: Laparoscopy, surgical, esophageal sphincter augmentation procedure, placement of sphincter augmentation device (i.e., magnetic band), including cruroplasty when performed</p> <p>43285: Removal of esophageal sphincter augmentation device</p> <p>Specifically, we request the above two procedures to be recommended for coverage for treatment of GERD. In total, over 50 peer-reviewed articles have been published on LINX, including 1 randomized control trial (RCT), 7 comparative, 11 single-arm, 3 meta-analysis. A few key published articles were not included in the sources of information in the basis for decision noncovered services. Therefore, to support reconsideration, additional sources of information that were not originally considered are included within this appeal. We believe that these new safety and efficacy data further reinforce the medical necessity of these procedures. In particular, you will find compelling evidence of long-term efficacy and safety of the LINX procedure, pursuant to the FDA approval. Furthermore, as a testimonial to its long-term outcomes, you will find a study recommending LINX be incorporated into the practice of National Health Service of UK following acceptable business plan and compliance.</p> | <p><i>comparative data. Single-arm (non-comparative) studies would not be included under usual HERC procedures except when they are summarized in systematic reviews.</i></p> <p><i>The SRs by Chen et al. (k = 4) and Skubleny et al. (k = 3) were identified in our search, but these were less comprehensive than the SR by Aiolfi et al. which summarizes 7 comparative observational studies of MSA, and includes all of the studies from both Skubleny et al. and Chen et al.</i></p> <p><i>Among the other manufacturer submitted citations, five are included in the Aiolfi et al. SR (Reynolds et al., 2015, Riegler et al., 2015, Warren et al., 2016, Louie et al., 2014, and Reynolds et al., 2016); seven are non-comparative studies (Ganz et al., 2016, Smith et al., 2017, Bonavina et al., 2013, Saino et al., 2015, Lipham et</i></p> |

HERC Coverage Guidance: Newer Interventional Procedures for GERD Disposition of Public Comments

| ID/# | Comment | Disposition |
|------|--|--|
| | | <p><i>al., 2015, Alicuben et al., 2018, and Prakash et al., 2017); and two are studies of LNF that are not pertinent to MSA (Draaisma et al., 2006 and Lafullarde et al., 2001).</i></p> <p><i>Thus, the subcommittee is confident that it has considered the totality of comparative evidence for MSA.</i></p> |
| B2 | <p>LINX® Reflux Management System-based MSA as an Alternative to LNF.</p> <p>LINX is a first line, fundic-sparing laparoscopic surgical treatment option for GERD. It consists of small, flexible band of titanium beads, with magnetic cores that augment the LES’ ability to close while allowing food and liquid to pass through to the stomach. Approved via the most rigorous FDA PMA process, LINX is safe and efficacious, reversible and reproducible, and associated with fewer side effects and complications compared to LNF. ¹⁻⁶</p> | <p><i>Thank you for your comments. We believe the relative merits of MSA and LNF were well summarized in the Aiofji SR which was considered by the subcommittee.</i></p> |
| B3 | <p>LINX® is supported by clinical societies and HTA bodies</p> <p>Determinations made by the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES), Federal Agency for Healthcare Research and Quality (AHRQ), and the American Society of General Surgeons (ASGS) are testimonials to support of this technology by gastroenterologists, surgeons, and foregut experts.^{2,3,7} In their most recent Safety and Effectiveness Analysis statement (2017), the SAGES Technology and Value Assessment Committee performed an exhaustive and detailed review of the published literature available for LINX, with dozens of studies cited and detailed. This report concluded that “implantation of the LINX® device should be covered and reimbursed by insurance for appropriate patients who meet the selection criteria as described above.”</p> | <p><i>It is misleading to assert that AHRQ supports the use of this technology. AHRQ stated that Horizon Scans should “...not be construed as endorsements or rejections of specific interventions.”</i></p> <p><i>The statement by SAGES is noted, but LINX is not mentioned in the official clinical practice guideline for surgical</i></p> |

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| | | <i>treatment of GERD that has been promulgated by SAGES. Similarly, the statement by ASGS is noted, but this organization does not appear to have a process for developing clinical practice guidelines.</i> |
| B4 | <p>Updated LINX® Evidence Not Considered Previously</p> <p><u>Complications of GERD</u></p> <ul style="list-style-type: none"> • LINX patients experienced long term improvement in regurgitation, PPI dependence, heartburn, and patient satisfaction.¹ <ul style="list-style-type: none"> ○ Patients experienced significant and sustained improvement in regurgitation up to 5 years.^{1,8,9} | <p><i>Thank you for your comments. We believe the relative merits of MSA and LNF were well summarized in the Aiolfi et al. SR, which was considered by the subcommittee. The data presented here were either included in the coverage guidance and informed the estimates of effect or are non-comparative studies as detailed above in B1.</i></p> <p><i>It should be noted that the NICE guidance issued in 2017 states that “...evidence of the long-term efficacy is inadequate,” and they recommend that the procedure “...only be used with special</i></p> |



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|------------------|--|--------------------|---------------------------|--------------------|---------------------------|---------|------------------|----------------------|-------|-------|---------|-----------------------|-------|-------|---------|------------------|----------------------|-------|-------|---------|-----------------------|-------|-------|--------|--------------|----------------------|-------|-------|--------|-----------------------|-------|-------|--|---|
| | <p>○ Significantly less gas/bloating with LINX and greater ability to belch and vomit with LINX.^{6,10}</p> <div style="text-align: center;"> <p>Propensity matched studies: LINX® vs Nissen fundoplication Side-effect profile, 1-year follow-up</p> <table border="1" style="margin: 10px auto; border-collapse: collapse;"> <caption>Side-effect profile, 1-year follow-up</caption> <thead> <tr> <th>Side Effect</th> <th>Study</th> <th>LINX Procedure (%)</th> <th>Nissen fundoplication (%)</th> <th>p-value</th> </tr> </thead> <tbody> <tr> <td rowspan="2">Ability to belch</td> <td>Warren, et al, N=114</td> <td>97.0%</td> <td>95.0%</td> <td>p<0.001</td> </tr> <tr> <td>Reynolds, et al, N=50</td> <td>91.5%</td> <td>74.5%</td> <td>p=0.028</td> </tr> <tr> <td rowspan="2">Ability to vomit</td> <td>Warren, et al, N=114</td> <td>88.0%</td> <td>40.0%</td> <td>p<0.001</td> </tr> <tr> <td>Reynolds, et al, N=50</td> <td>95.7%</td> <td>78.7%</td> <td>p<0.01</td> </tr> <tr> <td rowspan="2">Gas/bloating</td> <td>Warren, et al, N=114</td> <td>41.0%</td> <td>59.0%</td> <td>p<0.01</td> </tr> <tr> <td>Reynolds, et al, N=50</td> <td>27.7%</td> <td>36.3%</td> <td></td> </tr> </tbody> </table> </div> <p>○ Less regurgitation at one-year post-procedure.⁸</p> <p><u>GERD symptom scores</u></p> <ul style="list-style-type: none"> As measured by GERD-HRQL, LINX significantly improved quality of life.^{1,8,10,11,12,9,13} <p><u>Change in PPI therapy</u></p> <ul style="list-style-type: none"> Over 75% of patients experienced complete cessation of PPI at up to 5 years.^{1,8,10,11,12,9,13} Similar cessation of PPI usage found in patients undergoing LINX and LNF.⁵ <p><u>Harms</u></p> <ul style="list-style-type: none"> A 2014 study analyzed safety of LINX® procedure in the first 1000 patients worldwide at 82 institutions. While the intra/perioperative complication rates and device removal rates were 0.1% and 3.4%, respectively, the erosion rates were 0.1%.¹⁴ Most importantly, a recent seminal article analyzed FDA’s Manufacturer and User Facility Device Experience (MAUDE) database for data of 3283 patients who underwent LINX® procedure between March 2012-May | Side Effect | Study | LINX Procedure (%) | Nissen fundoplication (%) | p-value | Ability to belch | Warren, et al, N=114 | 97.0% | 95.0% | p<0.001 | Reynolds, et al, N=50 | 91.5% | 74.5% | p=0.028 | Ability to vomit | Warren, et al, N=114 | 88.0% | 40.0% | p<0.001 | Reynolds, et al, N=50 | 95.7% | 78.7% | p<0.01 | Gas/bloating | Warren, et al, N=114 | 41.0% | 59.0% | p<0.01 | Reynolds, et al, N=50 | 27.7% | 36.3% | | <p><i>arrangements for clinical governance, consent, and audit and research.”</i></p> |
| Side Effect | Study | LINX Procedure (%) | Nissen fundoplication (%) | p-value | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ability to belch | Warren, et al, N=114 | 97.0% | 95.0% | p<0.001 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Reynolds, et al, N=50 | 91.5% | 74.5% | p=0.028 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ability to vomit | Warren, et al, N=114 | 88.0% | 40.0% | p<0.001 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Reynolds, et al, N=50 | 95.7% | 78.7% | p<0.01 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Gas/bloating | Warren, et al, N=114 | 41.0% | 59.0% | p<0.01 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Reynolds, et al, N=50 | 27.7% | 36.3% | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

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| | <p>2016 across 165 institutes. The study showed no perioperative deaths and life-threatening complications, or device malfunctions.⁴ While the overall device explant rate was 2.7%, the erosion rate was 0.15%.</p> <ul style="list-style-type: none"> • Five-year reoperation rates were reported to be in the 13.1%-15.2% range with LNF,^{15,16} and in the 6.8%-7% range with LINX.^{1,11} • Importantly, another study that assessed the FDA’s MAUDE database for 9453 global implants of MSA device over the timeframe Feb 2007 – July 2017, reported device erosion of 0.3% with the median time to erosion of 26 months.¹⁷ • None of above studies reported MSA-associated mortality <p><u>Meta-analysis</u></p> <ul style="list-style-type: none"> • A recent meta-analysis of four databases compared LINX® to Nissen fundoplication by assessing 325 Nissen fundoplication and 299 LINX® procedures spanning 2005-2016. The publication reported that operating time with LINX® is in the 60-66 min range, which is 19.5%-29.5% shorter than Nissen fundoplication.¹⁸ <p><u>Recommendation of LINX® into the National Health Service (NHS) practice in UK</u></p> <p>In a study that prospectively evaluated 47 patients who underwent the LINX® procedure reported that reflux health-related quality of life (GERD-HRQL) was significantly improved after the procedure and maintained at one- and two-year (P < 0.0001) follow-up.¹⁹ Drug dependency went from 100% at baseline to 2.6% and 8.7% after one and two years. Importantly, the cost of the implant was offset against savings made from reduced usage of surgical equipment, operating time, inpatient stay/readmission.</p> <p>As such, the authors recommended LINX® to be incorporated into NHS practice.</p> | |
| B5 | <p>Coverage Reconsideration</p> <p>We believe that the completion of two FDA trials providing significant long term follow up, as well as multiple studies, peer-reviewed articles, and support of key medical societies and HTA bodies indicate that the MSA has withstood appropriate scrutiny, and can no longer be considered experimental/investigational. As such, it should be considered a part of the armamentarium in the proven and effective surgical treatment of GERD in appropriate patients.</p> | <i>Thank you for your comments.</i> |

HERC Coverage Guidance: Newer Interventional Procedures for GERD Disposition of Public Comments

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| | We would be happy to further discuss this with you and support your efforts for evidence-based review of coverage guidance and answer any questions that you may have as you consider this request. Thank you for your consideration. | |

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Temporary Percutaneous Mechanical Circulatory Support with Impella Devices

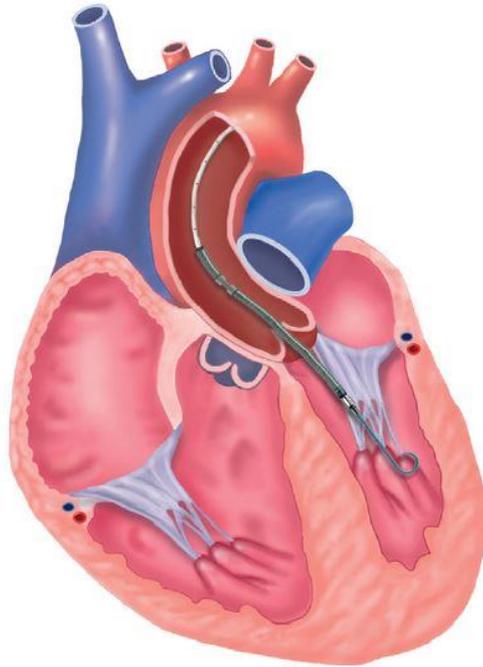
Draft Coverage Guidance for VbBS Consideration

January 17, 2019

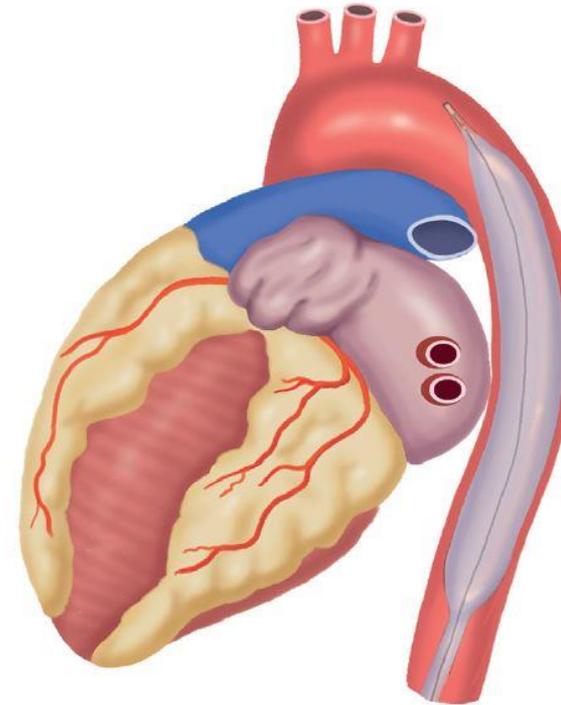
Background

- Temporary mechanical circulatory support (e.g., Impella) is used in patients with cardiogenic shock or who are undergoing elective high-risk coronary interventions
- Intra-aortic balloon pump (IABP) is the most frequently used ventricular assist device (since 1960s) because of ease of insertion and use
 - IABPs appear ineffective
- Impella may offer greater augmentation of cardiac output and left ventricular unloading
 - Decreasing myocardial oxygen consumption and pulmonary capillary wedge pressure, theoretically reducing the size of a myocardial infarction

Background



Impella device



Intra-aortic balloon pump

Source: Ouweneel et al., 2017

Impella has a small pump at one end of a thin, flexible tube with the other end connected to a system outside the body that controls pump rate

Background

- Impella has 5 models: 2.5, CP (or 3.5), RP, 5.0/LD
 - Most frequently used devices are Impella 2.5 and 5.0, capable of increasing cardiac output by up to 2.5 and 5.0 L/min, respectively
- Most Impella devices can be placed percutaneously through the femoral artery (or femoral vein for Impella RP)
 - Impella 5.0 typically requires an arterial cut-down procedure, and the Impella LD is placed during open chest procedures

Scope Statement

- Populations
 - Adults with cardiogenic shock or refractory heart failure (from right heart failure, left heart failure, or biventricular failure) and adults undergoing high-risk percutaneous coronary interventions (PCI)
- Interventions
 - Temporary percutaneous mechanical circulatory support devices (Impella)

Scope Statement

- Comparators
 - Usual care, inotropes, other forms of active circulatory support (i.e., IABP or more permanent left ventricular assist devices), extracorporeal membrane oxygenation (ECMO)

Scope Statement

- Critical Outcomes
 - Mortality
 - Major adverse cardiovascular events
- Important Outcomes
 - Successful bridge to transplantation or bridge to recovery
 - Length of hospitalization
 - Harms

Scope Statement

Key Questions

1. What is the comparative effectiveness of temporary percutaneous mechanical circulatory support in the management of adults with heart failure or cardiogenic shock, or undergoing high-risk PCI?
2. Does the comparative effectiveness of temporary percutaneous mechanical circulatory support vary by:
 - a. Indication for left ventricular support
 - b. Patient characteristics
 - c. Left ventricular function
 - d. Right ventricular function
 - e. Comorbid conditions
 - f. Device flow rate
 - g. Timing and duration of Impella placement
3. What are the harms of temporary percutaneous mechanical circulatory support?

Evidence Sources

- Health Quality Ontario review (2017)
 - High-quality systematic review and health technology assessment of the benefits and harms of Impella for high-risk PCI or cardiogenic shock
- Ait Ichou et al. (2017)
 - Fair-quality systematic review of the effectiveness and safety of Impella devices in patients undergoing high-risk PCI or with cardiogenic shock
- Ouweneel et al. (2017)
 - Briefly reported meta-analysis of 3 small RCTs of Impella compared to IABP in patients with cardiogenic shock

Evidence Review: High-risk PCI

- Health Quality Ontario review (2017)
 - Included studies of high-risk PCI
 - 1 RCT (PROTECT II)
 - 2 comparative observational studies
 - 8 non-comparative observational studies
 - Authors assessed the risk of bias in the RCT to be moderate because of insufficient statistical power, concern for selection bias, and early termination of the trial due to futility
 - Comparative observational studies were limited by selection bias, insufficient adjustment for confounding, and high rates of loss to follow-up

Evidence Review: High-risk PCI

- Health Quality Ontario review (2017)
 - Results:
 - No difference in 30-day mortality or major adverse cardiac events (MACE) between Impella 2.5 and IABP for high-risk PCI (low strength of evidence)
 - No difference in bleeding or vascular complications between Impella 2.5 and IABP for high-risk PCI (very low strength of evidence)

Evidence Review: High-risk PCI

- Ait Ichou et al. (2017)
 - Review is mainly limited by incomplete reporting of risk of bias assessments
 - Included studies:
 - 4 RCTs
 - 2 comparative observational studies
 - 14 non-comparative observational studies
 - 3 of the RCTs at low risk of bias and 1 at high risk of bias
 - 2 comparative observational studies were considered to be at high risk of bias because of their design and the likelihood of confounding by indication
 - All non-comparative observational studies were regarded as having serious or critical risk of bias

Evidence Review: High-risk PCI

- Ait Ichou et al. (2017)
 - Authors concluded there were no differences in all-cause mortality between Impella and IABP, but noted a possible reduction in major adverse events at 90 days in a per-protocol analysis of the PROTECTII trial
 - High levels of clinical heterogeneity in the studies and inadequate power to detect differences in clinical events
 - Larger RCTs are needed to better clarify the clinical effectiveness and safety of Impella, and 1 such trial is currently underway (DANSHOCK, NCT01633502)

Evidence Review: Cardiogenic Shock

- Health Quality Ontario review (2017)
 - Included studies for cardiogenic shock
 - 1 small RCT
 - 1 comparative observational study
 - 6 non-comparative observational studies
 - RCT was assessed to be at high risk of bias due to small sample size and imbalance in baseline characteristics
 - Comparative observational study was judged to be at moderate risk of bias because of selection bias and potential performance bias due to a high degree of physician discretion in managing the patients

Evidence Review: Cardiogenic Shock

- Health Quality Ontario review (2017)
 - Results:
 - No difference in 30-day mortality or MACE between Impella 2.5 and IABP for cardiogenic shock (low strength of evidence)
 - Significantly higher rate of hemolysis with Impella 2.5 compared to IABP for cardiogenic shock (low strength of evidence)
 - No difference in vascular complications between Impella 2.5 and IABP for cardiogenic shock (low strength of evidence)

Evidence Review: Cardiogenic Shock

- Ouweneel et al. (2017)
 - Meta-analysis of 3 small RCTs of Impella compared to IABP in patients with cardiogenic shock (n = 95)
 - No difference in all-cause mortality
 - At 30 days (RR 0.99, 95% CI 0.62 to 1.58)
 - At 6 months (RR 1.15, 95% CI 0.74 to 1.48)
 - No difference in left ventricle ejection fraction of survivors between the 2 groups at 2 to 6 months

Evidence Summary

- On the basis of a relatively small number of comparative studies, the use of Impella devices to support elective high-risk PCI or in the setting of ischemic cardiogenic shock did not improve clinical outcomes compared to IABP
- In some studies of patients with ischemic cardiogenic shock, Impella appears to increase the risk of bleeding and vascular complications compared to IABP, although a wide range of adverse effect rates are reported in the comparative studies
- There were no systematic reviews or RCTs of Impella in the setting of non-ischemic cardiogenic shock

GRADE Table: High-risk PCI

| Outcomes | Estimate of Effect for Outcome/ Confidence in Estimate |
|---|--|
| All-cause mortality (Critical outcome) | <p>No significant difference in all-cause mortality 7.6% for Impella vs. 5.9% for IABP at 30 days $p = 0.47$</p> <p>12.1% for Impella vs. 8.7% for IABP at 90 days $p = 0.244$</p> <p>●●○○ (Low confidence, based on 1 RCT, n = 448)</p> |

GRADE Table: High-risk PCI

| Outcomes | Estimate of Effect for Outcome/ Confidence in Estimate |
|---|--|
| Major adverse cardiovascular events (Critical outcome) | <p>No significant difference in composite outcome of major adverse events (including repeat revascularization): 35.1% for Impella vs. 40.1% for IABP at 30 days $p = 0.227$</p> <p>40.6% for Impella vs. 49.3% for IABP at 90 days $p = 0.066$</p> <p>●●○○ (Low confidence, based on 1 RCT, n = 448)</p> |

GRADE Table: High-risk PCI

| Outcomes | Estimate of Effect for Outcome/ Confidence in Estimate |
|---|---|
| Successful bridge to recovery (Important outcome) | Not applicable |
| Successful bridge to transplant (Important outcome) | Not applicable |
| Harms (Important outcome) | <p>No significant difference in major bleeding complications between Impella and IABP ●○○○ (Very low confidence, based on 1 observational study, n = 75)</p> <p>No significant difference in vascular complications between Impella and IABP ●○○○ (Very low confidence, based on 1 observational study, n = 75)</p> |

GRADE Table: Cardiogenic Shock

| Outcomes | Estimate of Effect for Outcome/ Confidence in Estimate |
|---|---|
| All-cause mortality (Critical outcome) | <p>No significant difference in all-cause mortality 40.8% for Impella vs. 41.3% for IABP at 30 days RR 0.99 (95% CI 0.62 to 1.58, p = 0.95)</p> <p>46.9% for Impella vs. 41.3% for IABP at 6 months RR 1.15 (95% CI 0.74 to 1.48, p = 0.53)</p> <p>●●○○ (Low confidence, based on 3 RCTs, n = 95)</p> |

GRADE Table: Cardiogenic Shock

| Outcomes | Estimate of Effect for Outcome/ Confidence in Estimate |
|---|---|
| Major adverse cardiovascular events (Critical outcome) | <p>No significant difference in major adverse cardiovascular events</p> <p>26% for Impella vs. 33% for IABP at 4 months $p = 0.74$</p> <p>37% for Impella vs. 47% for IABP at 12 months $p = 0.72$</p> <p>●○○○ (Very low confidence, based on 1 RCT, $n = 21$)</p> |

GRADE Table: Cardiogenic Shock

| Outcomes | Estimate of Effect for Outcome/ Confidence in Estimate |
|---|--|
| Successful bridge to recovery (Important outcome) | Insufficient data |
| Successful bridge to transplant (Important outcome) | Insufficient data |
| Harms (Important outcome) | <p>Range of reported vascular complications Impella: 3% to 25% IABP: 0% to 6.4% ●○○○ (Very low confidence, based on 4 studies, n = 222)</p> <p>Range of reported bleeding complications Impella: 8% to 38.4% IABP: 0% to 32.2% ●○○○ (Very low confidence, based on 5 studies, n = 272)</p> |

GRADE Table: PCI for acute myocardial infarction without cardiogenic shock

| Outcomes | Estimate of Effect for Outcome/ Confidence in Estimate |
|--|---|
| All-cause mortality (Critical outcome) | Insufficient data |
| Major adverse cardiovascular events (Critical outcome) | Insufficient data |
| Successful bridge to recovery (Important outcome) | Insufficient data |
| Successful bridge to transplant (Important outcome) | Insufficient data |
| Harms (Important outcome) | Insufficient data |

Payer Policies

- Washington State Medicaid Program
 - Provides coverage for FDA-approved percutaneous left ventricular assist devices for these indications:
 - Short-term circulatory support in cardiogenic shock
 - As an adjunct to PCI in the following high-risk patients:
 - Clients undergoing unprotected left main or last-remaining-conduit PCI with ejection fraction less than 35%
 - Clients with three vessel disease and diastolic ejection fraction less than 30%
- Medicare
 - No Medicare National Coverage Determination or Local Coverage Determinations were found for percutaneous mechanical circulatory support

Payer Policies

- Private Payers
 - Aetna provides coverage for Impella for these indications:
 - Short-term circulatory support in cardiogenic shock
 - As an adjunct to PCI in high-risk patients
 - Cigna provides the following coverage for Impella:
 - Up to 14 days in a child or adult with a BSA $\geq 1.5\text{m}^2$ for the treatment of acute right heart failure or decompensation following left ventricular assist device implantation, myocardial infarction, heart transplant, or open-heart surgery
 - For the treatment of cardiogenic shock for up to 6 hours
 - Moda requires prior authorization for left ventricular assist devices
 - Regence policy on ventricular assist devices states that the policy does not address the use of percutaneous ventricular assist devices, which may be considered medically necessary

Guidelines

- 3 guidelines were identified:
 - Guideline for the Management of ST-Elevation Myocardial Infarction published in 2013 by the American College of Cardiology Foundation and American Heart Association Task Force on Practice Guidelines
 - Alternative left ventricular assist devices for circulatory support may be considered in patients with refractory cardiogenic shock
 - Clinical Expert Consensus Statement on the Use of Percutaneous Mechanical Circulatory Support Devices in Cardiovascular Care published by the Society for Cardiovascular Angiography and Interventions, American College of Cardiology Foundation, Heart Failure Society of America, and Society for Thoracic Surgery
 - Percutaneous mechanical circulatory support may be considered in carefully selected patients with severe hemodynamically unstable cardiovascular presentations

Guidelines

- 3 guidelines were identified: (*cont.*)
 - 2013 International Society for Heart and Lung Transplantation Guidelines for Mechanical Circulatory Support
 - Use of temporary mechanical support should be strongly considered in patients with multiorgan failure, sepsis, or on mechanical ventilation to allow successful optimization of clinical status and neurologic assessment prior to placement of a long-term mechanical circulatory support device

Public Comment

- 8 public comments submitted, mostly from providers, and Abiomed (manufacturer of Impella)
- Comment: Concerns about comparing Impella 2.5 to those with greater circulatory support
 - Response: All Impella devices except the 5.0 (which requires an arterial cutdown) were included; no evidence was found on differential effectiveness of various models
- Comment: Some non-comparative studies showed improvements in outcomes
 - Response: Standard methodology does not include non-comparative case series

Public Comment

- Comment: Clinical practice guidelines recommend use of these devices; some guidelines were not included
 - Response: Guidelines from International Society for Heart & Lung Transplant were added to the coverage guidance; the other cited recommendations were not from guidelines
- Comment: Commercial payers cover this
 - Response: C5, E3, G2 Standard methodology is to include the coverage policies for Medicare, WA Medicaid, Aetna, Cigna and Moda, and these policies were considered in the deliberations of this coverage guidance.

Public Comment

- Comment: There are several RCTs of IABP in patients with cardiogenic shock that have shown no clinical benefit of IABP
 - Response: IABP was a comparator in all of the RCTs of Impella for ischemic cardiogenic shock, and Impella was not found to be superior to IABP
- Comment: Patients who are inoperable (i.e., not eligible for coronary artery bypass graft) could only have PCI with Impella support
 - Response: The studies did not include subgroup analyses for inoperable patients; with the noncoverage recommendation, patients may not have access to PCI without Impella support; however, there may be no mortality benefit to PCI for many of these patients

Discussion: High-risk PCI

Values and Preferences

Patients would strongly prefer interventions that improve their outcomes (with regard to death or MACE) and have fewer harms. The mechanism by which this is achieved (i.e., IABP or Impella) is unlikely to be important to patients. There is likely to be low variability in these values and preferences.

Resource Allocation

Impella is extremely expensive and may cost as much as 20 times more than an IABP.

Discussion: High-risk PCI

Balance of Benefits and Harms

We have low confidence that there is no difference between Impella and IABP in terms of all cause-mortality and MACE and very low confidence of no difference in complications between major bleeding and vascular complications. The balance suggests no net benefit and no net harms based on limited evidence.

Discussion: High-risk PCI

Rationale

We make a recommendation against coverage for elective high-risk PCI in stable coronary artery disease because there appears to be no benefit for Impella over IABP and no difference in complications. Impella is much more expensive than the comparator, and patient values and preferences would not lean toward either direction. It is a strong recommendation because Impella appears to offer no benefit over the current standard of care at a much greater cost.

Discussion: High-risk PCI

Temporary percutaneous mechanical circulatory support with Impella devices is not recommended for coverage in elective high-risk percutaneous coronary intervention (PCI) for patients with stable coronary artery disease (*weak recommendation*).

Discussion: Cardiogenic Shock

Values and Preferences

Patients would strongly prefer interventions that improve their outcomes (with regard to death or MACE) and have fewer harms. The mechanism by which this is achieved (i.e., IABP or Impella) is unlikely to be important to patients. There is likely to be low variability in these values and preferences.

Resource Allocation

Impella is extremely expensive and may be as much as 20 times more than an IABP.

Other Considerations

There was insufficient evidence to include in the GRADE table for non-ischemic cardiogenic shock. There were no studies found examining patients bridging to LVAD or transplant.

Discussion: Cardiogenic Shock

Balance of Benefits and Harms

We have low confidence that there is no difference between Impella and IABP in terms of all-cause mortality, and very low confidence that there is no difference in MACE. We have very low confidence that significant harms (such as bleeding, stroke, and vascular events) are greater with Impella compared to IABP. The evidence reviewed suggests that the balance is neutral to negative for Impella in ischemic cardiogenic shock. Insufficient evidence was found for non-ischemic cardiogenic shock to make an assessment of the balance of benefits and harms.

Discussion: Cardiogenic Shock

Rationale

We recommend against Impella for ischemic cardiogenic shock because of a lack of proven benefit, possibility of greater significant harms, and significant increase in resource allocation compared to IABP. No studies were found for non-ischemic cardiogenic shock, and so the recommendation applies to all types of cardiogenic shock.

Patients who are candidates for LVAD or bridging to a transplant are an unstudied population, but it might be appropriate to consider Impella on an individual basis, based on expert opinion.

Discussion: Cardiogenic Shock

Temporary percutaneous mechanical circulatory support with Impella devices is recommended for coverage (*weak recommendation*) only for patients with cardiogenic shock who might be candidates for left ventricular assist device (LVAD) (destination therapy) or transplant (bridge to transplant), AND an advanced heart failure and transplant cardiologist agrees that Impella should be used as a bridge to a decision for LVAD or a transplant.

Discussion: High-risk elective PCI

Values and Preferences

Patients with acute myocardial infarction would likely strongly prefer an intervention thought to result in survival benefit. If Impella were thought to be necessary to allow revascularization for high-risk patients, their preferences would likely be in favor of Impella.

Resource Allocation

Impella is extremely expensive and may be as much as 20 times more than an IABP.

Discussion: High-risk elective PCI

Other Considerations

An RCT of these populations is feasible, however, given widespread use of Impella in current practice, might not be performed.

Balance of Benefits and Harms

There is insufficient evidence to evaluate the balance of benefits and harms. Expert opinion indicates that protected PCI might provide a significant survival benefit in patients with NSTEMI who are not eligible for CABG.

Discussion: High-risk elective PCI

Rationale

Patients with NSTEMI and low ejection fraction are an unstudied population for whom expert opinion indicates that protected PCI might provide a significant survival benefit and PCI might not otherwise be done without Impella devices. Although resource allocation and the lack of evidence would argue against coverage, values and preferences and expert opinion suggest in this carefully selected population a true survival benefit may exist. The coverage recommendation is weak because of the lack of evidence.

There was no evidence in patients with NSTEMI without shock, but this population is very likely to be revascularized regardless of their risk. Given that the availability of Impella is unlikely to change whether or not a patient is going to be revascularized, and given the lack of evidence and the high cost, a recommendation is not made for coverage.

Discussion: High-risk elective PCI

Temporary percutaneous mechanical circulatory support with Impella devices during PCI is recommended for coverage (*weak recommendation*) only for patients with acute myocardial infarction when all of the following conditions are met:

- NSTEMI without cardiogenic shock
- A heart team discussion determines that the patient needs revascularization with CABG or PCI
- Two cardiothoracic surgeons are consulted and agree that the patient is inoperable (i.e., surgeons are not willing to perform CABG, but agree that revascularization is indicated)
- Patient has complex left main or last remaining conduit disease
- Ejection fraction less than 30%

Health Evidence Review Commission (HERC)

Coverage Guidance: Temporary Percutaneous Mechanical Circulatory Support with Impella Devices

DRAFT for 1/17/2019 VbBS/HERC meeting materials

HERC Coverage Guidance

Temporary percutaneous mechanical circulatory support with Impella devices is not recommended for coverage in elective high-risk percutaneous coronary intervention (PCI) for patients with stable coronary artery disease (*weak recommendation*).

Temporary percutaneous mechanical circulatory support with Impella devices during PCI is recommended for coverage (*weak recommendation*) only for patients with acute myocardial infarction when all of the following conditions are met:

- NSTEMI without cardiogenic shock
- A heart team discussion determines the patient needs revascularization with CABG or PCI
- Two cardiothoracic surgeons are consulted and agree the patient is inoperable (i.e., are not willing to perform CABG but agree revascularization is indicated)
- Patient has complex left main or last remaining conduit disease
- Ejection fraction (EF) < 30%

Temporary percutaneous mechanical circulatory support with Impella devices is recommended for coverage (*weak recommendation*) for patients with cardiogenic shock only in patients who may be candidates for Left Ventricular Assist Device (LVAD) (destination therapy) or transplant (bridge to transplant), AND an advanced heart failure and transplant cardiologist agrees that Impella should be used as a bridge to decision for LVAD or transplant.

Note: Definitions for strength of recommendation are in Appendix A. GRADE Table Element Description. Rationales for each recommendation appear below in the GRADE table.

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Rationale for development of coverage guidances and multisector intervention reports

Coverage guidances are developed to inform coverage recommendations for public and private health plans in Oregon as plan administrators seek to improve patients' experience of care, population health, and the cost-effectiveness of health care. In the era of public and private sector health system transformation, reaching these goals requires a focus on maximizing the benefits and minimizing the harms and costs of health interventions.

HERC uses the following principles in selecting topics for its reports to guide public and private payers:

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

HERC bases its reports on a review of the best available research applicable to the intervention(s) in question. For coverage guidances, which focus on diagnostic and clinical interventions, evidence is evaluated using an adaptation of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology. For more information on coverage guidance methodology, see Appendix A.

Multisector interventions can be effective ways to prevent, treat, or manage disease at a population level. In some cases, HERC has reviewed evidence and identified effective interventions, but has not made formal coverage recommendations when these policies are implemented in settings other than traditional health care delivery systems because effectiveness could depend on the environment in which the intervention is implemented.

GRADE Table

HERC develops recommendations by using the concepts of the GRADE system. GRADE is a transparent and structured process for developing and presenting evidence and for performing the steps involved in developing recommendations. The table below lists the elements that determine the strength of a recommendation. HERC reviews the evidence and assesses each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Estimates of effect are derived from the evidence presented in this document. Assessments of confidence are from the published systematic reviews and meta-analyses, where available and judged to be reliable.

In some cases, no systematic reviews or meta-analyses encompass the most current literature. In those cases, HERC may describe the additional evidence or alter the assessments of confidence in light of all available information. Such assessments are informed by clinical epidemiologists from the Center for Evidence-based Policy. Unless otherwise noted, statements regarding resource allocation, values and preferences, and other considerations are the assessments of HERC, as informed by the evidence reviewed, public testimony, and subcommittee discussion.

Recommendations for coverage are based on the balance of benefit and harms, resource allocation, values and preferences, and other considerations. See Appendix A for more details about the factors that constitute the GRADE table.

DRAFT

GRADE Table

Should temporary percutaneous mechanical circulatory support (i.e., Impella) be recommended for coverage for elective high-risk percutaneous coronary intervention?

| Outcomes | Estimate of Effect for Outcome/ <i>Confidence in Estimate</i> | Resource Allocation | Values and Preferences | Other Considerations |
|---|--|---|--|----------------------|
| All-cause mortality <i>(Critical outcome)</i> | <p>No significant difference in all-cause mortality 7.6% for Impella vs. 5.9% for intra-aortic balloon pump (IABP) at 30 days p = 0.47</p> <p>12.1% for Impella vs. 8.7% for IABP at 90 days p = 0.244</p> <p>●○○○ <i>(Low confidence, based on 1 RCT, n = 448)</i></p> | <p>Impella is extremely expensive and may cost as much as 20 times more than an IABP.</p> | <p>Patients would strongly prefer interventions that improve their outcomes (with regard to death or major adverse cardiac events [MACE]) and have fewer harms. The mechanism by which this is achieved (i.e., IABP or Impella) is unlikely to be important to patients. There is likely to be low</p> | |

Should temporary percutaneous mechanical circulatory support (i.e., Impella) be recommended for coverage for elective high-risk percutaneous coronary intervention?

| Outcomes | Estimate of Effect for Outcome/ <i>Confidence in Estimate</i> | Resource Allocation | Values and Preferences | Other Considerations |
|---|---|---------------------|--|----------------------|
| Major adverse cardiovascular events <i>(Critical outcome)</i> | No significant difference in composite outcome of major adverse events (including repeat revascularization): 35.1% for Impella vs. 40.1% for IABP at 30 days p = 0.227 40.6% for Impella vs. 49.3% for IABP at 90 days p = 0.066 ●●○○ <i>(Low confidence, based on 1 RCT, n = 448)</i> | | variability in these values and preferences. | |
| Successful bridge to recovery <i>(Important outcome)</i> | Not applicable | | | |
| Successful bridge to transplant <i>(Important outcome)</i> | Not applicable | | | |

Should temporary percutaneous mechanical circulatory support (i.e., Impella) be recommended for coverage for elective high-risk percutaneous coronary intervention?

| Outcomes | Estimate of Effect for Outcome/ <i>Confidence in Estimate</i> | Resource Allocation | Values and Preferences | Other Considerations |
|--|---|---------------------|------------------------|----------------------|
| Harms <i>(Important outcome)</i> | <p>No significant difference in major bleeding complications between Impella and IABP ●○○○ <i>(Very low confidence, based on 1 observational study, n = 75)</i></p> <p>No significant difference in vascular complications between Impella and IABP ●○○○ <i>(Very low confidence, based on 1 observational study, n = 75)</i></p> | | | |

Balance of benefits and harms: We have low confidence that there is no difference between Impella and IABP in terms of all cause-mortality and MACE and very low confidence of no difference in complications between major bleeding and vascular complications. The balance suggests no net benefit and no net harms based on limited evidence.

Rationale: We make a recommendation against coverage for elective high-risk PCI in stable coronary artery disease because there appears to be no benefit for Impella over IABP and no difference in complications. Impella is much more expensive than the comparator, and patient values and preferences would not lean toward either direction. It is a strong recommendation because Impella appears to offer no benefit over the current standard of care at a much greater cost.

Should temporary percutaneous mechanical circulatory support (i.e., Impella) be recommended for coverage for elective high-risk percutaneous coronary intervention?

| Outcomes | Estimate of Effect for Outcome/ <i>Confidence in Estimate</i> | Resource Allocation | Values and Preferences | Other Considerations |
|---|--|---------------------|------------------------|----------------------|
| <p>Recommendation: Temporary percutaneous mechanical circulatory support with Impella devices is not recommended for coverage for patients receiving elective high-risk percutaneous coronary interventions (<i>weak recommendation</i>).</p> <p>Temporary percutaneous mechanical circulatory support with Impella devices during PCI is recommended for coverage for patients with acute non-ST-elevation myocardial infarction (NSTEMI) without cardiogenic shock (<i>weak recommendation</i>) when all of the following conditions are met:</p> <ul style="list-style-type: none"> • A heart team discussion determines the patient needs revascularization with CABG or PCI. • Two cardiothoracic surgeons are consulted and agree the patient is inoperable (i.e. are not willing to perform CABG but agree revascularization is indicated). • Patient has complex left main or last remaining conduit disease • Ejection fraction (EF) < 30% | | | | |

Note: GRADE table elements are described in Appendix A. A GRADE Evidence Profile is in Appendix B.

Should temporary percutaneous mechanical circulatory support (i.e., Impella) be recommended for coverage for cardiogenic shock?

| Outcomes | Estimate of Effect for Outcome/ Confidence in Estimate | Resource Allocation | Values and Preferences | Other Considerations |
|---|---|--|---|--|
| All-cause mortality <i>(Critical outcome)</i> | No significant difference in all-cause mortality 40.8% for Impella vs. 41.3% for IABP at 30 days RR 0.99 (95% CI 0.62 to 1.58, p = 0.95) 46.9% for Impella vs. 41.3% for IABP at 6 months RR 1.15 (95% CI 0.74 to 1.48, p = 0.53) ●●○○ (Low confidence, based on 3 RCTs, n = 95) | Impella is extremely expensive and may be as much as 20 times more than an IABP. | Patients would strongly prefer interventions that improve their outcomes (with regard to death or MACE) and have fewer harms. The mechanism by which this is achieved (i.e., IABP or Impella) is unlikely to be important to patients. There is likely to be low variability in these values and preferences. | There was insufficient evidence to include in the GRADE table for non-ischemic cardiogenic shock. There were no studies found examining patients bridging to LVAD or transplant. |
| Major adverse cardiovascular events <i>(Critical outcome)</i> | No significant difference in major adverse cardiovascular events 26% for Impella vs. 33% for IABP at 4 months p = 0.74 37% for Impella vs. 47% for IABP at 12 months p = 0.72 ●○○○ (Very low confidence, based on 1 RCT, n = 21) | | | |
| Successful bridge to recovery <i>(Important outcome)</i> | Insufficient data | | | |

Should temporary percutaneous mechanical circulatory support (i.e., Impella) be recommended for coverage for cardiogenic shock?

| Outcomes | Estimate of Effect for Outcome/ Confidence in Estimate | Resource Allocation | Values and Preferences | Other Considerations |
|--|--|---------------------|------------------------|----------------------|
| Successful bridge to transplant (Important outcome) | Insufficient data | | | |
| Harms (Important outcome) | <p>Range of reported vascular complications Impella: 3% to 25% IABP: 0% to 6.4% ●○○○ (Very low confidence, based on 4 studies, n = 222)</p> <p>Range of reported bleeding complications Impella: 8% to 38.4% IABP: 0% to 32.2% ●○○○ (Very low confidence, based on 5 studies, n = 272)</p> | | | |

Balance of benefits and harms: We have low confidence that there is no difference between Impella and IABP in terms of all-cause mortality, and very low confidence that there is no difference in MACE. We have very low confidence that significant harms (such as bleeding, stroke, and vascular events) are greater with Impella compared to IABP. The evidence reviewed suggests that the balance is neutral to negative for Impella in ischemic cardiogenic shock. Insufficient evidence was found for nonischemic cardiogenic shock to make an assessment of the balance of benefits and harms.

Rationale: We recommend against Impella for ischemic cardiogenic shock because of a lack of proven benefit, possibility of greater significant harms, and significant increase in resource allocation compared to IABP. No studies were found for non-ischemic cardiogenic shock, and so the recommendation applies to all types of cardiogenic shock.

Patients who are candidates for LVAD or bridging to transplant are an unstudied population but may be appropriate to be considered for Impella on an individual basis, based on expert opinion.

Should temporary percutaneous mechanical circulatory support (i.e., Impella) be recommended for coverage for cardiogenic shock?

| Outcomes | Estimate of Effect for Outcome/ <i>Confidence in Estimate</i> | Resource Allocation | Values and Preferences | Other Considerations |
|--|--|---------------------|------------------------|----------------------|
| <p>Recommendation: Temporary percutaneous mechanical circulatory support with Impella devices is recommended for coverage (<i>weak recommendation</i>) in cardiogenic shock only in patients who may be candidates for LVAD (destination therapy) or transplant (bridge to transplant), AND an advanced heart failure and transplant cardiologist agrees that Impella should be used as a bridge to decision for LVAD or transplant.</p> | | | | |

DRAFT

Should temporary percutaneous mechanical circulatory support (i.e., Impella) be recommended for coverage to support PCI for acute myocardial infarction without cardiogenic shock?

| Outcomes | Estimate of Effect for Outcome/ <i>Confidence in Estimate</i> | Resource Allocation | Values and Preferences | Other Considerations |
|---|--|--|---|---|
| All-cause mortality <i>(Critical outcome)</i> | Insufficient data | Impella is extremely expensive and may be as much as 20 times more than an IABP. | Patients with acute myocardial infarction would likely strongly prefer an intervention thought to result in survival benefit. If Impella were thought to be necessary to allow revascularization for high-risk patients, their preferences would likely be in favor of Impella. | A RCT of these populations is feasible, however, given widespread use of Impella in current practice, may not be performed. |
| Major adverse cardiovascular events <i>(Critical outcome)</i> | Insufficient data | | | |
| Successful bridge to recovery <i>(Important outcome)</i> | Insufficient data | | | |
| Successful bridge to transplant <i>(Important outcome)</i> | Insufficient data | | | |
| Harms <i>(Important outcome)</i> | Insufficient data | | | |

Balance of benefits and harms: There is insufficient evidence to evaluate the balance of benefits and harms. Expert opinion indicates protected PCI may provide a significant survival benefit in patients with NSTEMI who are not eligible for CABG.

Should temporary percutaneous mechanical circulatory support (i.e., Impella) be recommended for coverage to support PCI for acute myocardial infarction without cardiogenic shock?

| Outcomes | Estimate of Effect for Outcome/ <i>Confidence in Estimate</i> | Resource Allocation | Values and Preferences | Other Considerations |
|--|--|---------------------|------------------------|----------------------|
| <p>Rationale: Patients with NSTEMI and low ejection fraction are an unstudied population for whom expert opinion indicates protected PCI may provide a significant survival benefit and may not otherwise be done without Impella devices. While resource allocation and the lack of evidence would argue against coverage, values and preferences and expert opinion suggests in this carefully selected population a true survival benefit may exist. The coverage recommendation is weak because of the lack of evidence.</p> <p>There was no evidence in patients with STEMI without shock, but this population is very likely to be revascularized regardless of their risk. Given that the availability of Impella is unlikely to change whether or not a patient is going to get revascularized, the lack of evidence, and the high cost, a recommendation is not made for coverage.</p> | | | | |
| <p>Recommendation: Temporary percutaneous mechanical circulatory support with Impella devices during PCI is recommended for coverage (<i>weak recommendation</i>) only for patients with acute myocardial infarction when all of the following conditions are met:</p> <ul style="list-style-type: none"> • NSTEMI without cardiogenic shock • A heart team discussion determines the patient needs revascularization with CABG or PCI • Two cardiothoracic surgeons are consulted and agree the patient is inoperable (i.e., are not willing to perform CABG but agree revascularization is indicated) • Patient has complex left main or last remaining conduit disease • Ejection fraction (EF) < 30% | | | | |

Note: GRADE table elements are described in Appendix A. A GRADE Evidence Profile is in Appendix B.

Background

Temporary mechanical circulatory support may be needed in patients with cardiogenic shock or who are undergoing elective high-risk coronary interventions. The intra-aortic balloon pump (IABP) has been the most frequently used ventricular assist device since its introduction in the 1960s because of the ease of insertion and use (Ait Ichou, 2017). For some patients in severe cardiogenic shock with a systolic aortic pressure that cannot be improved to more than 60 mmHg by vasopressors, the IABP might not provide sufficient circulatory support (Ait Ichou, 2017). Temporary percutaneous mechanical circulatory support devices, such as Impella, offer greater augmentation of cardiac output and left ventricular unloading. It has been hypothesized that these hemodynamic advantages would result in improved clinical outcomes. Other circulatory support devices (not in scope for this Coverage Guidance) require open surgery or septal puncture, and could be appropriate for longer-term use.

Indications

Temporary percutaneous mechanical circulatory support devices are indicated for patients in cardiogenic shock and those undergoing elective high-risk percutaneous coronary interventions (PCI).

Technology Description

Impella is a device for mechanical circulatory support that has a small pump at one end of a thin, flexible tube and is implanted through an artery in the leg. The other end of the tube is connected to a control system outside the body that controls the pump rate (Health Quality Ontario, 2017). Impella works by increasing the maximal blood flow by unloading blood from the left ventricle into the ascending aorta, resulting in improved coronary perfusion pressure and end-organ perfusion. In addition to increasing cardiac output, it also decreases myocardial oxygen consumption and pulmonary capillary wedge pressure, potentially reducing the size of a myocardial infarction and accelerating its recovery (Ait Ichou, 2017).

Impella has four models: 2.5, CP (or 3.5), RP, and 5.0/LD (Abiomed, 2018). The most frequently used devices, Impella 2.5 and 5.0, are capable of increasing cardiac output by up to 2.5 and 5.0 L/min, respectively (Ait Ichou, 2017). Most Impella devices can be placed percutaneously through the femoral artery (or the femoral vein for Impella RP), but the Impella 5.0 typically requires an arterial cut-down procedure, and the Impella LD is placed during open chest procedures (Ait Ichou, 2017).

In 2015, the U.S. Food and Drug Administration (FDA) granted premarket approval to Impella 2.5 (FDA, 2015). This approval order stated that Impella was indicated for temporary (< 6 hours) ventricular support during high-risk PCI performed in elective or urgent, hemodynamically stable patients with severe coronary artery disease and depressed left ventricular ejection fraction (LVEF) (FDA, 2015). A 2016 supplemental order from the FDA approved Impella for patients experiencing ongoing cardiogenic shock immediately (< 48 hours) after acute myocardial infarction or open-heart surgery for the Impella Ventricular Support Systems (FDA, 2016). A February 2018 supplemental order expanded the indications to include patients with ongoing cardiogenic shock in the setting of cardiomyopathy, including peripartum cardiomyopathy or myocarditis (FDA, 2018).

Evidence Review

Our search identified two systematic reviews and one briefly reported meta-analysis for inclusion. Because of the small number of comparative studies of Impella and because of the incomplete overlap of included studies (see Table 1) in the reviews, the individual comparative studies included in those reviews are summarized in Tables 2-4. The characteristics of the individual comparative studies are summarized in Table 2 and their relevant outcomes are summarized in Tables 3 and 4.

The Health Quality Ontario review (2017) is a high-quality systematic review and health technology assessment of the benefits and harms of Impella for high-risk PCI or cardiogenic shock. For the high-risk PCI group, the authors identified one randomized controlled trial (RCT) (O'Neill et al., 2012), two comparative observational studies (Boudoulas et al., 2012; Schwartz et al., 2011), and eight non-comparative observational studies. The authors assessed the risk of bias in the RCT to be moderate because of insufficient statistical power, concern for selection bias, and early termination of the trial due to futility. The comparative observational studies were limited by selection bias, insufficient adjustment for confounding, and high rates of loss to follow-up.

For the cardiogenic shock group, the authors identified one small RCT (Seyfarth et al., 2011), one comparative observational study (Manzo-Silberman et al., 2013), and six non-comparative observational studies. The RCT was assessed to be at high risk of bias due to small sample size and the risk of model misclassification, as well as imbalance in baseline characteristics. The comparative observational study was judged to be at moderate risk of bias because of selection bias (including an imbalance in baseline LVEF between cohorts) and potential treatment bias due to a high degree of physician discretion in managing the patients. The relevant results from the included comparative studies are summarized in Tables 3 and 4 below. Applying a GRADE methodology, the authors of the review concluded that there was:

- No difference in 30-day mortality or MACE between Impella 2.5 and IABP for high-risk PCI (low strength of evidence)
- No difference in bleeding or vascular complications between Impella 2.5 and IABP for high-risk PCI (very low strength evidence)
- No difference in 30-day mortality or MACE between Impella 2.5 and IABP for cardiogenic shock (low strength of evidence)
- Significantly higher rate of hemolysis with Impella 2.5 compared to IABP for cardiogenic shock (low strength of evidence)
- No difference in vascular complications between Impella 2.5 and IABP for cardiogenic shock (low strength of evidence)

The review by Ait Ichou et al. (2017) is a fair-quality systematic review of the effectiveness and safety of Impella devices in patients undergoing high-risk PCI. The review is mainly limited by incomplete reporting of risk of bias assessments. The authors identified four RCTs (Seyfarth et al., 2008; O'Neill et al., 2012; Ouweneel et al., 2017b; Ouweneel et al., 2016), two comparative observational studies (Boudoulas et al., 2012; Schwartz et al., 2011), and 14 non-comparative observational studies, for a total of 1,287 patients. The authors judged three of the RCTs to be at low risk of bias and one (Ouweneel et al., 2016) to be at high risk of bias due to early termination and changes to inclusion criteria during recruitment. The two comparative observational studies were considered to be at high risk of bias

because of their design and the likelihood of confounding by indication. All of the non-comparative observational studies were regarded as having serious or critical risk of bias. The relevant results from the included comparative studies are summarized in Tables 3 and 4 below.

Overall, the authors concluded that there were no differences in all-cause mortality between Impella and IABP, but noted a possible reduction in major adverse events at 90 days in a per-protocol analysis of the PROTECTII trial (O'Neill et al., 2012). They observed high levels of clinical heterogeneity in the studies and that most studies were inadequately powered to detect differences in clinical events. Finally, the authors asserted the need for larger RCTs to better clarify the clinical effectiveness and safety of Impella, and noted that one such trial (DANSHOCK, NCT01633502) is currently underway.

The review by Ouweneel et al. (2017a) is a briefly reported meta-analysis that combines the results of the three small RCTs of Impella compared to IABP in patients with cardiogenic shock (Seyfarth et al., 2008; O'Neill et al., 2012; Ouweneel et al., 2017b; Ouweneel et al., 2016). The total population of these studies was 95 patients. In the meta-analysis (it is not stated whether a fixed or random effects model was used), there was no difference in all-cause mortality at 30 days (RR 0.99, 95% CI 0.62 to 1.58) or at six months (RR 1.15, 95% CI 0.74 to 1.48). There was also no difference in LVEF of survivors between the two groups at two to six months.

Our search did not identify any additional RCTs published after the most recent systematic review (Ait Ichou et al., 2017). Additionally, the search did not identify any systematic reviews or RCTs examining the use of Impella in the setting of acute non-ischemic cardiogenic shock.

Evidence Summary

On the basis of a relatively small number of comparative studies, the use of Impella devices to support elective high-risk PCI or in the setting of ischemic cardiogenic shock did not improve clinical outcomes compared to IABP. In some studies of patients with ischemic cardiogenic shock, Impella appears to increase the risk of bleeding and vascular complications compared to IABP, although a wide range of adverse effect rates are reported in the comparative studies. There were no systematic reviews or RCTs of Impella in the setting of non-ischemic cardiogenic shock.

Table 1. Studies Included in Systematic Reviews

| | Seyfarth 2008 (Risk of bias assessment) | O’Neill 2012 (Risk of bias assessment) | Ouweneel 2017b (Risk of bias assessment) | Ouweneel 2016 (Risk of bias assessment) | Schwartz 2011 (Risk of bias assessment) | Manzo-Silberman 2013 (Risk of bias assessment) | Boudoulas 2012 (Risk of bias assessment) |
|-----------------------------|--|---|---|--|--|---|---|
| Ait Ichou 2017 | X (Low) | X (Low) | X (Low) | X (High) | X (Serious) | | X (Serious) |
| Ouweneel 2017a | X (Not rated) | | X (Not rated) | X (Not rated) | | | |
| Health Quality Ontario 2017 | X (High) | X (Moderate) | | | X (Moderate) | X (Moderate) | X (Moderate) |

Table 2. Characteristics of Individual Comparative Studies

| | Study type Setting | Population | Intervention (N) Comparator (N) |
|----------------|---|---|--|
| Seyfarth 2008 | Randomized controlled trial 2 centers in Germany | Adults with acute myocardial infarction < 48 hours and cardiogenic shock | Impella 2.5 (13) IABP (13) |
| Schwartz 2011 | Retrospective cohort Single center | Adults undergoing high-risk PCI supported with Impella, IABP, or TandemHeart between 2008 and 2010 | Impella 2.5 (13) TandemHeart (32) IABP (5) |
| Boudoulas 2012 | Retrospective cohort Single center | All patients with ACS undergoing high-risk PCI supported with Impella 2.5 or IABP between 2008 and 2010 | Impella 2.5 (12) IABP (62) |

| | Study type Setting | Population | Intervention (N) Comparator (N) |
|----------------------|---|---|------------------------------------|
| O'Neill 2012 | Randomized controlled trial 112 centers in the US, Canada, and Germany | Adults undergoing high-risk elective PCI (defined as unprotected left main or last patent vessel with LVEF < 35% or 3 vessel disease with LVEF < 30%) | Impella 2.5 (225) IABP (223) |
| Manzo-Silberman 2013 | Retrospective cohort Single center | Adult survivors of out-of-hospital cardiac arrest and post-resuscitation shock supported with Impella or IABP after coronary angiography between 2007 and 2010 | Impella 2.5 (35) IABP (43) |
| Ouweneel 2017b | Randomized controlled trial | Adults with STEMI and severe cardiogenic shock (SBP < 90 mmHg for more than 30 minutes or need for inotropes or vasopressors to maintain SBP > 90 mmHg), and requiring mechanical ventilation | Impella CP (24) IABP (24) |
| Ouweneel 2016 | Randomized controlled trial 5 centers | Adults with anterior STEMI and cardiogenic pre-shock (defined as HR > 100 and/or SBP < 100 mmHg with clinical signs of shock) | Impella 2.5 (11) IABP (9) |

Table 3. Outcomes from RCTs

| | All-cause mortality, 30 days | All-cause mortality, 90-360 days | MACE, 30 days | MACE, 90-360 days | Adverse events |
|-------------------------|------------------------------|----------------------------------|---------------|-------------------|--|
| Seyfarth 2008 n = 26 | 46% Impella 46% IABP | NR | NR | NR | 1 case of acute limb ischemia following Impella removal RBC transfusion requirement (mean) 2.6 units Impella |

| | All-cause mortality, 30 days | All-cause mortality, 90-360 days | MACE, 30 days | MACE, 90-360 days | Adverse events |
|--------------------------|------------------------------|--|--|---|--|
| | | | | | 1.2 units IABP |
| O'Neill 2012 n = 448 | 7.6% Impella 5.9% IABP | 12.1% Impella 8.7% IABP (at 90 days) | 35.1% Impella 40.1% IABP (outcome defined as major adverse events) | 40.6% Impella 49.3% IABP (outcome defined as major adverse events at 90 days) | NR |
| Ouweneel 2017b n = 48 | 46% Impella 50% IABP | 50% Impella 50% IABP | NR | NR | Stroke 4.2% Impella 4.2% IABP Major vascular event 4.2% Impella 0% IABP Bleeding 33.3% Impella 8.3% IABP |
| Ouweneel 2016 n = 21 | NR | 26% Impella 11% IABP (at 4 months) | NR | 26% Impella 33% IABP (at 4 months) | Severe vascular events 25% Impella 0% IABP |

| | All-cause mortality, 30 days | All-cause mortality, 90-360 days | MACE, 30 days | MACE, 90-360 days | Adverse events |
|--|------------------------------|----------------------------------|---------------|---|--|
| | | | | 37% Impella 47% IABP (at 12 months) | Need for renal replacement therapy 18% Impella 0% IABP Ventricular arrhythmias 8% Impella 11% IABP Stroke 8% Impella 0% IABP Severe bleeding 8% Impella 0% IABP Hemolysis 8% Impella 0% IABP |

Table 4. Outcomes of Comparative Observational Studies

| | All-cause mortality, 30 days | All-cause mortality, 90-360 days | MACE, 30 days | MACE, 90-360 days | Adverse events |
|--------------------------|---|----------------------------------|--|-------------------|--|
| Schwartz 2011 n = 50 | 15% Impella 13% TandemHeart 0% IABP | NR | 15% Impella 19% TandemHeart 40% IABP | NR | Limb ischemia 0% Impella 6% TandemHeart 0% IABP Major bleeding 31% Impella 13% TandemHeart 20% IABP |
| Boudoulas 2012 n = 75 | In-hospital mortality 0% Impella 20.9% IABP | 15.3% Impella 25.8% IABP | NR | NR | Vascular complications 15.3% Impella 6.4% IABP Leg ischemia 15.3% Impella 3.2% IABP Mesenteric ischemia 0% Impella 1.6% IABP |

| | All-cause mortality, 30 days | All-cause mortality, 90-360 days | MACE, 30 days | MACE, 90-360 days | Adverse events |
|--------------------------------|--|----------------------------------|---------------|-------------------|--|
| | | | | | <p>Aortic rupture</p> <p>0% Impella 1.6% IABP</p> <p>Bleeding</p> <p>38.4% Impella 32.2% IABP</p> <p>CVA</p> <p>0% Impella 3.2% IABP</p> <p>Bacteremia</p> <p>0% Impella 4.7% IABP</p> |
| Manzo-Silberman 2013 n = 78 | <p>Survival at day 3</p> <p>34% Impella 67% IABP</p> <p>Survival with CPC score 1 at 28 days</p> | NR | NR | NR | <p>Hemolytic anemia</p> <p>6% Impella 0% IABP</p> <p>Sustained ventricular arrhythmias</p> |

| | All-cause mortality, 30 days | All-cause mortality, 90-360 days | MACE, 30 days | MACE, 90-360 days | Adverse events |
|--|------------------------------|----------------------------------|---------------|-------------------|--|
| | 23% Impella 29.5% IABP | | | | 17% Impella 24% IABP Bleeding requiring transfusion 26% Impella 9% IABP Vascular complications 3% Impella 2% IABP |

Policy Landscape

Payer Coverage Policies

Medicaid

The [Washington State Medicaid Program billing guide](#) (7/1/2018) provides coverage for FDA-approved percutaneous left ventricular assist devices for these indications:

- Providing short-term circulatory support in cardiogenic shock
- As an adjunct to PCI in the following high-risk patients:
 - Clients undergoing unprotected left main or last-remaining-conduit PCI with ejection fraction less than 35%
 - Clients with three vessel disease and diastolic ejection fraction less than 30%

Medicare

No Medicare National Coverage Determination (NCD) or Local Coverage Determinations were found for percutaneous mechanical circulatory support. The [NCD on ventricular assist devices](#) provides coverage only for ventricular assist devices that are surgically attached to one or both intact ventricles.

Private Payers

The Aetna [policy on ventricular assist devices](#) (last review 3/22/18) provides coverage for Impella for these indications:

- Providing short-term circulatory support in cardiogenic shock
- As an adjunct to PCI in the following high-risk patients:
 - Persons undergoing unprotected left main or last-remaining-conduit PCI with ejection fraction less than 35%
 - Persons with three vessel disease and diastolic ejection fraction less than 30%.

The Cigna [policy on ventricular assist devices and percutaneous cardiac support systems](#) (effective 2/15/18) provides the following coverage:

- Impella RP System for up to 14 days in a child or adult with a BSA $\geq 1.5\text{m}^2$ for the treatment of acute right heart failure or decompensation following left ventricular assist device implantation, myocardial infarction, heart transplant, or open-heart surgery
- Impella Recover LP 2.5 Percutaneous Cardiac Support System, Impella 5.0 Catheters, or Impella 2.5 Plus for the treatment of cardiogenic shock for up to six hours

Moda's [list of procedures and services requiring prior authorization](#) (updated 7/1/2018) includes left ventricular assist devices.

The Regence [policy on ventricular assist devices and total artificial hearts](#) (effective 2/1/2018) states that this policy does not address the use of percutaneous ventricular assist devices, which may be considered medically necessary.

Recommendations from Others

Three guidelines were identified that include recommendations on temporary percutaneous mechanical circulatory support:

- Guideline for the Management of ST-Elevation Myocardial Infarction published in 2013 by the American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) Task Force on Practice Guidelines (O'Gara et al., 2013)
- Clinical Expert Consensus Statement on the Use of Percutaneous Mechanical Circulatory Support Devices in Cardiovascular Care published by the Society for Cardiovascular Angiography and Interventions, American College of Cardiology Foundation, Heart Failure Society of America, and Society for Thoracic Surgery (Rihal et al., 2015)
- The 2013 International Society for Heart and Lung Transplantation Guidelines for Mechanical Circulatory Support (Feldman et al., 2013)

The ACCF/AHA guideline includes a recommendation that alternative left ventricular assist devices for circulatory support may be considered in patients with refractory cardiogenic shock (O'Gara et al., 2013). The guideline from the Society for Cardiovascular Angiography and Interventions states that percutaneous mechanical circulatory support may be considered in carefully selected patients with severe hemodynamically unstable cardiovascular presentations. Suggested indications for percutaneous mechanical circulatory support include complications of acute myocardial infarction, severe heart failure in the setting of non-ischemic cardiomyopathy, acute cardiac allograft failure, post-transplant right ventricle failure, refractory arrhythmias, high-risk ablation of ventricular tachycardia, and high-risk PCI (Rihal et al., 2015).

The following recommendation from the International Society for Heart and Lung Transplantation guidelines is based on level of evidence C, or consensus agreement: “The use of temporary mechanical support should be strongly considered in patients with multiorgan failure, sepsis, or on mechanical ventilation to allow successful optimization of clinical status and neurologic assessment prior to placement of a long-term [mechanical circulatory support device]” (Feldman et al., 2013, p. 165)

Quality Measures

No quality measures were identified when searching the National Quality Measures Clearinghouse for percutaneous mechanical circulatory support or Impella.

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Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

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Appendix A. GRADE Table Element Descriptions

| Element | Description |
|-------------------------------|---|
| Balance of benefits and harms | The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. An estimate that is not statistically significant or has a confidence interval crossing a predetermined clinical decision threshold will be downgraded. |
| Quality of evidence | The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted |
| Resource allocation | The higher the costs of an intervention—that is, the greater the resources consumed in the absence of likely cost offsets—the lower the likelihood that a strong recommendation is warranted |
| Values and preferences | The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted |
| Other considerations | Other considerations include issues about the implementation and operationalization of the technology or intervention in health systems and practices within Oregon. |

Strong recommendation

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

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

Weak recommendation

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

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

Confidence in estimate rating across studies for the intervention/outcome

Assessment of confidence in estimate includes factors such as risk of bias, precision, directness, consistency and publication bias.

High: The subcommittee is very confident that the true effect lies close to that of the estimate of the effect. Typical sets of studies are RCTs with few or no limitations and the estimate of effect is likely stable.

Moderate: The subcommittee is moderately confident in the estimate of effect: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.

Low: The subcommittee's confidence in the estimate of effect is limited: The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

Very low: The subcommittee has very little confidence in the estimate of effect: The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

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Appendix B. GRADE Evidence Profile

| Quality Assessment (Confidence in Estimate of Effect) for Elective High-Risk PCI | | | | | | | |
|--|-----------------|--------------|---------------|--------------|-------------|---------------|------------------|
| No. of Studies | Study Design(s) | Risk of Bias | Inconsistency | Indirectness | Imprecision | Other Factors | Quality |
| All-cause mortality | | | | | | | |
| 1 | RCT | Moderate | Not serious | Not serious | Serious | | Low ●●○○ |
| Major adverse events | | | | | | | |
| 1 | RCT | Moderate | Not serious | Not serious | Serious | | Low ●●○○ |
| Bridge to recovery | | | | | | | |
| N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Bridge to transplant | | | | | | | |
| N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Harms | | | | | | | |
| 1 | Observational | Moderate | Not serious | Not serious | Not serious | | Very low ●○○○ |

| Quality Assessment (Confidence in Estimate of Effect) for Ischemic Cardiogenic Shock | | | | | | | |
|--|-------------------------------|------------------|---------------|--------------|--------------|---------------|-------------------|
| No. of Studies | Study Design(s) | Risk of Bias | Inconsistency | Indirectness | Imprecision | Other Factors | Quality |
| All-cause mortality | | | | | | | |
| 3 | RCTs | Moderate to high | Not serious | Not serious | Serious | | Low ●●○○ |
| Major adverse events | | | | | | | |
| 1 | RCT | High | N/A | Not serious | Very serious | | Very low ●○○○ |
| Bridge to recovery | | | | | | | |
| 0 | N/A | N/A | N/A | N/A | N/A | N/A | Insufficient data |
| Bridge to transplant | | | | | | | |
| 0 | N/A | N/A | N/A | N/A | N/A | N/A | Insufficient data |
| Harms | | | | | | | |
| 4 | Mix of RCTs and observational | Moderate to high | Serious | Not serious | Very serious | | Very low ●○○○ |

Appendix C. Methods

Scope Statement

Populations

Adults with cardiogenic shock or refractory heart failure (from right heart failure, left heart failure, or biventricular failure) and adults undergoing high-risk percutaneous coronary interventions (PCI)

Population scoping notes: None

Interventions

Temporary percutaneous mechanical circulatory support devices (Impella)

Intervention exclusions: Devices not marketed in the U.S., TandemHeart, extracorporeal membrane oxygenation (ECMO).

Comparators

Usual care, inotropes, other forms of active circulatory support (i.e., intra-aortic balloon pumps or more permanent left ventricular assist devices), extracorporeal membrane oxygenation (ECMO)

Outcomes

Critical: Mortality, major adverse cardiovascular events

Important: Successful bridge to transplantation or bridge to recovery, length of hospitalization, harms

Considered but not selected for the GRADE table: None

Key Questions

KQ1: What is the comparative effectiveness of temporary percutaneous mechanical circulatory support in the management of adults with heart failure or cardiogenic shock, or undergoing high-risk PCI?

KQ2: Does the comparative effectiveness of temporary percutaneous mechanical circulatory support vary by:

- a. Indication for left ventricular support
- b. Patient characteristics
- c. Left ventricular function
- d. Right ventricular function
- e. Comorbid conditions
- f. Device flow rate
- g. Timing and duration of Impella placement

KQ3: What are the harms of temporary percutaneous mechanical circulatory support?

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, and technology assessments that meet the criteria for the scope described above. Searches of core sources were limited to citations published after 2013.

The following core sources were searched:

- Agency for Healthcare Research and Quality (AHRQ)
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Online Library)
- Institute for Clinical and Economic Review (ICER)
- Medicaid Evidence-based Decisions Project (MED)
- National Institute for Health and Care Excellence (NICE)
- Tufts Cost-effectiveness Analysis Registry
- Veterans Administration Evidence-based Synthesis Program (ESP)
- Washington State Health Technology Assessment Program

A MEDLINE® search was also conducted to identify systematic reviews, meta-analyses, and technology assessments, using the search terms Impella, ventricular support system, and axial flow pumps. The search was limited to publications in English published since 2013. In addition, a MEDLINE® search was conducted for randomized controlled trials published after 2013.

Searches for clinical practice guidelines were limited to those published since 2013. A search for relevant clinical practice guidelines was also conducted using MEDLINE® and the following sources:

- Australian Government National Health and Medical Research Council (NHMRC)
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Centers for Disease Control and Prevention (CDC), Community Preventive Services
- National Guidelines Clearinghouse
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Preventive Services Task Force (USPSTF)
- Veterans Administration/Department of Defense (VA/DoD) Clinical Practice Guidelines

Inclusion/Exclusion Criteria

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

Appendix D. Applicable Codes

| CODES | DESCRIPTION |
|------------------|---|
| CPT Codes | |
| 33990 | Insertion of ventricular assist device, percutaneous including radiological supervision and interpretation; arterial access only |
| 33991 | Insertion of ventricular assist device, percutaneous including radiological supervision and interpretation; both arterial and venous access, with transeptal puncture |
| 33992 | Removal of percutaneous ventricular assist device at separate and distinct session from insertion |
| 33993 | Repositioning of percutaneous ventricular assist device with imaging guidance at separate and distinct session from insertion |

Note: Inclusion on this list does not guarantee coverage.

CG - Impella Devices

Question: How should the Coverage Guidance *Temporary Percutaneous Mechanical Circulatory Support With Impella Devices* be applied to the Prioritized List?

Question source: EbGS

Issue: EbGs approved a draft coverage guidance on Impella devices. There was extensive discussion between subcommittee members and the appointed expert about the challenges with the existing evidence and recommended subpopulations that are most likely to benefit. Subcommittee members discussed the fact that these devices have widely become standard of care despite the evidence base. They approved a draft coverage guidance that recommends coverage in 2 populations, high risk patients with acute NSTEMI, and those with cardiogenic shock who are candidates for bridge to transplant or LVAD.

EbGS Draft Coverage Guidance Box Language

Temporary percutaneous mechanical circulatory support with Impella devices is not recommended for coverage in elective high-risk percutaneous coronary intervention (PCI) for patients with stable coronary artery disease (*weak recommendation*).

Temporary percutaneous mechanical circulatory support with Impella devices during PCI is recommended for coverage (*weak recommendation*) only for patients with acute myocardial infarction when all of the following conditions are met:

- NSTEMI without cardiogenic shock
- A heart team discussion determines the patient needs revascularization with CABG or PCI
- Two cardiothoracic surgeons are consulted and agree the patient is inoperable (i.e., are not willing to perform CABG but agree revascularization is indicated)
- Patient has complex left main or last remaining conduit disease
- Ejection fraction (EF) < 30%

Temporary percutaneous mechanical circulatory support with Impella devices is recommended for coverage (*weak recommendation*) for patients with cardiogenic shock only in patients who may be candidates for Left Ventricular Assist Device (LVAD) (destination therapy) or transplant (bridge to transplant), AND an advanced heart failure and transplant cardiologist agrees that Impella should be used as a bridge to decision for LVAD or transplant.

Current Prioritized List Status:

| CODES | DESCRIPTION | | |
|-----------|--|---|--|
| CPT Codes | | Current Placement | Code History |
| 33990 | Insertion of ventricular assist device, percutaneous including radiological supervision and interpretation; arterial access only | 82 MYOCARDITIS, PERICARDITIS, AND ENDOCARDITIS 98 HEART FAILURE 264 CONGESTIVE HEART FAILURE, CARDIOMYOPATHY, MALIGNANT ARRHYTHMIAS, AND COMPLEX CONGENITAL | Added in 2013 as part of CPT 2012 code review without discussion |

CG - Impella Devices

| | | HEART DISEASE | |
|-------|--|---------------|------|
| 33991 | Insertion of ventricular assist device, percutaneous including radiological supervision and interpretation; both arterial and venous access, with transseptal puncture | 82,98,264 | Same |
| 33992 | Removal of percutaneous ventricular assist device at separate and distinct session from insertion | 82,98,264 | Same |
| 33993 | Repositioning of percutaneous ventricular assist device with imaging guidance at separate and distinct session from insertion | 82,98,264 | Same |

Illustrative ICD-10 codes

| Code | Code Description | Line Placement |
|----------|---|---|
| R57.0 | Cardiogenic shock | 69 ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION |
| T81.11XA | Postprocedural cardiogenic shock, initial encounter | 69 |
| T81.11XD | Postprocedural cardiogenic shock, subsequent encounter | 69 |
| I20.0 | Unstable angina | 69 |
| I20.1 | Angina pectoris with documented spasm | 189 CHRONIC ISCHEMIC HEART DISEASE |
| I20.8 | Other forms of angina pectoris | 189 |
| I20.9 | Angina pectoris, unspecified | 189 |
| I25.110 | Atherosclerotic heart disease of native coronary artery with unstable angina pectoris | 69,264 |
| I25.11X | Atherosclerotic heart disease of native coronary artery with angina pectoris... | 189 |
| I21.XX | ST elevation (STEMI) myocardial infarction | 69 |
| I21.4 | Non-ST elevation (NSTEMI) myocardial infarction | 69 |
| I22.2 | Subsequent non-ST elevation (NSTEMI) myocardial infarction | 69 |

Recommendations:

- 1) Add 33990, 33991, 33992, and 33993 to Line 69 ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION

CG - Impella Devices

- a. 33991 was out of scope, but confirmed with the expert that this is only for Tandem Heart and is no longer likely to be in use.
- 2) Remove 33990 and 33991 from Lines 82,98,264
- 3) Do NOT add 33990 to Line 189 CHRONIC ISCHEMIC HEART DISEASE as this would be for elective high-risk percutaneous coronary intervention (PCI) for patients with stable coronary artery disease
- 4) Create a new guideline note
GUIDELINE NOTE XXX TEMPORARY PERCUTANEOUS MECHANICAL CIRCULATORY SUPPORT WITH IMPELLA DEVICES
Line 69

Temporary percutaneous mechanical circulatory support with Impella devices is included on Line 69 only in the two following circumstances:

- 1) During percutaneous coronary intervention (PCI) in patients with acute myocardial infarction when all of the following conditions are met:
 - NSTEMI without cardiogenic shock
 - A heart team discussion determines the patient needs revascularization with coronary artery bypass graft (CABG) or PCI
 - Two cardiothoracic surgeons are consulted and agree the patient is inoperable (i.e., are not willing to perform CABG but agree revascularization is indicated)
 - Patient has complex left main or last remaining conduit disease
 - Ejection fraction (EF) < 30%
- 2) In patients with cardiogenic shock in patients who may be candidates for Left Ventricular Assist Device (LVAD) (destination therapy) or transplant (bridge to transplant), AND an advanced heart failure and transplant cardiologist agrees that Impella should be used as a bridge to decision for LVAD or transplant.

Temporary percutaneous mechanical circulatory support with Impella devices is not covered for elective high-risk PCI for patients with stable coronary artery disease.

HERC Coverage Guidance: Temporary Percutaneous Mechanical Circulatory Support with Impella Devices Disposition of Public Comments

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Discussion Table

| IDs/#s | Summary of Issue | Subcommittee Response |
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| A2, AF | Concerns about comparing Impella 2.5 to those with greater circulatory support | All Impella devices except the 5.0 (which requires an arterial cutdown) were included within scope, and evidence suggesting differential effectiveness would have been considered, if found. |
| A3, G2 | Protect II clinical trial showed trend of improvement | Given the severity of outcomes, and the arguments from proponents of these devices that they are effective, one would expect to see significant differences in critical outcomes when these devices were used. The studies did not show that Impella is superior to intra-aortic balloon pump (IABP). |
| A5 | Concern that the coverage guidance only addresses ischemic cardiogenic shock and does not address non-ischemic cardiogenic shock | There was very limited evidence on non-ischemic cardiogenic shock. Therefore, there is a recommendation against coverage for non-ischemic cardiogenic shock. |
| A5 | Role of Impella as a bridge to left ventricular assist device (LVAD) | A weak recommendation for coverage has been made for selected patients, including bridge to LVAD where an advanced heart failure |

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Temporary Percutaneous Mechanical Circulatory Support with Impella Devices
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| IDs/#s | Summary of Issue | Subcommittee Response |
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| | | and transplant cardiologist agrees that Impella should be used as a bridge to decision for LVAD or transplant. |
| A5 | The strength of the evidence is too weak to make a conclusion against the use of Impella | The strength of the evidence is too weak to make a recommendation for coverage. However, patients who are candidates for LVAD or bridging to transplant are an unstudied population but may be appropriate to be considered for Impella on an individual basis, based on expert opinion. |
| A5 | Guidelines recommend use of these devices | These guidelines were included in the considerations. |
| B2, C2, D3, G2 | Evidence from some uncontrolled studies shows improvements in outcomes | Non-comparative case series do not provide adequate comparative evidence of benefit. In the RCT, there was no difference in acute kidney injury. |
| C4, F4 | Missing guidelines | The 2013 ISHLT guideline was added to the coverage guidance. |
| C5, E3, G2 | Commercial payers cover this | The coverage policies of commercial and other payers were considered in the deliberations of this coverage guidance. |
| D2, D3, F3, G2, H2 | Balloon pumps do not work well | The evidence review found no differences in outcomes between balloon pumps and Impella devices. |
| E1, E2 | The Impella 5.0/Impella LD heart pumps are effective | These devices were outside the scope of this coverage guidance. |
| G2 | Concerns with the included systematic review | The systematic review of concern was judged to be of value, and the results of the individual studies were individually included. |

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| G4, H3 | The cost-effectiveness considerations do not take into account the costs of other treatments and their complications | A cost-effectiveness analysis was not performed nor included. In considering resources, the comparative cost of the device was considered. If the Impella devices are effective, the higher cost may be justified in a coverage decision. |
| A3, B1, D2, D3, D4, F2 | Patients who are inoperable (not eligible for coronary artery bypass graft (CABG)) and could only have PCI with Impella support | Studies did not specifically examine patients who had inoperable disease. These patients were included in the studied population, but no subgroup analysis was performed. The subcommittee acknowledges that with a noncoverage recommendation patients may not have access to PCI without Impella support. However, there is no mortality benefit to PCI for most of these patients, and no evidence that Impella would actually make PCI safer for these patients. |

Commenters

| Identification | Stakeholder |
|----------------|--|
| A | Todd A. Caulfield, MD, FACC, FSCAI, Medical Director, Quality; Medical Director, Providence Heart Clinics – West, Providence Heart Institute (PHI); Medical Staff President, Providence St. Vincent Medical Center <i>[Submitted September 25, 2018]</i> |
| B | Kevin H. Thompson, DO <i>[Submitted October 1, 2018]</i> |
| C | Richard C Padgett, MD <i>[Submitted October 8, 2017]</i> |
| D | Stephen L. Cook., MD <i>[Submitted October 10, 2017]</i> |
| E | Eric B. Kirker, MD <i>[Submitted October 10, 2018]</i> |
| F | Mark G. Moran, MD, FACC, FSCAI <i>[Submitted October 11, 2018]</i> |
| G | Stacey Bunk, MS, CPC, CCC, FABC, Director, Reimbursement & Healthcare Economics, ABIOMED, Inc. <i>[Submitted October 11, 2018]</i> |
| H | Amish J. Desai, MD <i>[Submitted October 12, 2018]</i> |

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Public Comments

| ID/# | Comment | Disposition |
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| A1 | <p>Thank you for calling our attention to the recent HERC document addressing Temporary Percutaneous Mechanical Circulatory Support with Impella Devices. As cardiac providers at a high volume center which regularly utilizes Impella technology, we believe that the conclusions of the HERC document are not justified nor reflective of our current practice.</p> | <p><i>Thank you for your comments. HERC and its subcommittees value the input and experience of providers who use the interventions under review.</i></p> |
| A2 | <p><u>Technologic Advance</u></p> <p>As you are aware, the field of mechanical circulatory support (MCS) has been rapidly evolving. The device referenced in the majority of studies cited is the Impella 2.5, smaller than the currently used Impella CP and Impella 5.0. There is much greater circulatory support with these devices, and in no way should outcomes with the Impella 2.5 be considered comparable to those obtained with devices which generate greater support.</p> | <p><i>The review included randomized trials and comparative observational studies using any of the Impella family of devices. One of the included studies used Impella CP. We did not find any data that directly compared Impella 2.5 to other Impella devices with respect to the outcomes included in the review. Lastly, the Impella 5.0, because it requires an arterial cutdown procedure for placement was not regarded, in the strictest sense, as a percutaneous procedure.</i></p> |
| A3 | <p><u>PCI</u></p> <p>The first point to emphasize is that the utilization of Impella devices is very carefully considered and in no way reflexive. Only a very small percentage of PCI cases performed, even in the setting of high risk PCI, including those with cardiogenic shock and STEMI, utilize Impella. Careful case selection occurs, and patients frequently require complete support from the Impella device during the procedure (i.e., develop PEA) due to the severity of the disease being undertaken. These are inoperable patients that have no other options, and with our expertise, outcomes are excellent. Data supporting this assertion can be provided if helpful. Additionally this advance</p> | <p><i>The subcommittee had extensive discussion about the potential role of Impella to support PCI procedures that would not otherwise be offered or undertaken, as well as its value for patients who are not candidates for surgical revascularization. However, the subcommittee believed that the available randomized and comparative observational evidence (including the PROTECT II study) did not establish that Impella support was superior to IABP. The studies did not include selection criteria for</i></p> |

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| | <p>has allowed us to treat patients who previously went to CABG. This allows more conservative patient selection for our surgical colleagues, and at this institution, surgical outcomes for CABG are the best in our large system. Again, data to support this is available upon request.</p> <p>It is imperative to note that our professional societies and guidelines support the use of the Impella device in carefully selected patients in highly experienced centers. Additionally, the Protect II clinical trial did reveal a strong trend and possibly a statistically significant benefit when patients were followed for 90 days or more. This is the same data set that was used to support the recommendation against Impella use in the high risk PCI population.</p> | <p><i>"inoperable patients" (some 'inoperable patients' were included in the study but no subgroup analysis was performed.</i></p> |
| A4 | <p>Secondly please recognize that the HERC recommendation on this topic is only weak in strength. In reviewing Appendix A, there can be two outcomes from this: In Favor and Against. We recommend voting against this recommendation at this time. In the language provided, there will be undesirable effects that outweigh the desirable effects, but acknowledge that further research could lead to a different conclusion.</p> <p>A document is attached to provide objective support for this conclusion, based on our own review of the data, some of which was also used to support the position presented in this HERC document.</p> | <p><i>Thank you for your comments.</i></p> |
| A5 | <p><u>Cardiogenic shock</u></p> <p>The analysis is limited to patients with ischemic cardiogenic shock (CS). Notably, on the basis of the IABP-SHOCK II trial, the IABP has been downgraded to a Class IIIA recommendation for use in CS in the most recent European re-vascularization and NSTEMI ACS guidelines. Moreover, by limiting its focus on ischemic CS, the HERC document excludes a large proportion of cardiogenic shock due to non-ischemic etiologies, including decompensated chronic HF.</p> | <p><i>Our search did not identify any systematic reviews or randomized controlled trials of Impella for non-ischemic cardiogenic shock.</i></p> <p><i>We agree that the utility of IABP has been called into question by large-scale trials. However, IABP was a comparator in all of the randomized controlled trials of</i></p> |

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| | <p>The HERC review notes that there are insufficient data on the use of Impella as a bridge to recovery, bridge to transplant, and, presumably, bridge to durable left ventricular assist device. As the only advanced heart failure center in Oregon, these are important indications for use of temporary mechanical circulatory support (MCS).</p> <p>The studies cited in the HERC review are largely based on a comparison of the Impella 2.5 vs IABP. The Impella 2.5 provides inadequate hemodynamic support for moderate to severe cardiogenic shock, and thus the lack of clinic benefit vs IABP is not surprising. At Providence and most advanced HF programs, the Impella CP or 5.0 are utilized for shock. In support of this practice, the American Heart Association Scientific Statement on Contemporary Management of Cardiogenic Shock (Circulation 2017;136:e232-e268) suggests that the IABP be “considered in CS patients with acute mitral regurgitation or a ventricular septal defect, and <i>it can be considered in select patients with profound CS when other MCS devices are not available, are contraindicated, or cannot be placed.</i>” (emphasis added) The axillary 5.0 Impella approach, with which we have considerable experience at Providence, provides the important benefit of enabling ambulation during prolonged mechanical support and has been used to successful bridge a number of patients to durable LVAD or recovery.</p> <p>The management of cardiogenic shock is rapidly evolving. The population is markedly heterogeneous and notoriously difficult to study. The strength of studies cited in the HERC analysis are, in our opinion, too weak to make conclusions against the use of Impella or other temporary MCS, in cardiogenic shock. Systems of care, including the implementation of a shock team approach to rapidly identify appropriate candidates and implement MCS prior to irreversible organ dysfunction; after action reviews; and quality analysis; are critical components to the rational implementation of these technologies.</p> | <p><i>Impella for ischemic cardiogenic shock and the results did not show improved outcomes from Impella.</i></p> <p><i>Unfortunately, comparative evidence of Impella in ischemic cardiogenic shock is quite limited. However, one of the studies included in the review did compare Impella CP to IABP.</i></p> |

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| A6 | <p>In conclusion, we thank you for calling our attention to this HERC coverage guidance. As we increasingly provide advanced cardiac care to this diverse, vulnerable patient population, please understand that the Impella device is an integral part of the care that we provide and is standard of care in our community and nationwide.</p> | <p><i>Thank you for your comments.</i></p> |
| B1 | <p>I am an interventional cardiologist at Salem Hospital in Salem, OR and have supported a number of my patients with a Percutaneous Ventricular Assist Device (pVADs) when there is or where there exists the potential for acute cardiac instability and for whom this treatment was medically necessary.</p> <p>Therefore, I am requesting reconsideration of the above-referenced coverage policy.</p> <p>There is a robust and growing body of literature and practice guidelines that substantiate the benefits of pVAD therapy.</p> <p>I can relay many patient stories where the PVAD, and specifically Impella therapy, saved the lives of my patients who were in critical condition and would not have survived without this emergent intervention. It has allowed high risk patients to receive critical procedures thereby extending the quality and duration of their lives.</p> <p>I regularly bill, and receive payment for the insertion of the Impella when used as support during both elective and emergent percutaneous coronary interventions. (I am also aware the hospital in which I perform the Impella procedure receives payment under the appropriate MS-DRG by these same payers).</p> <p>That is because these payers recognize the cost benefit of this therapy while providing the following clinical benefits: reduction in major adverse events, protection from acute kidney injury (AKI), and reduces repeat revascularizations.</p> | <p><i>Thank you for your comments. HERC and its subcommittees value the input and experience of providers who use the interventions under review. The subcommittee bases its decisions on the best available evidence. In this case, the randomized trials of Impella failed to show a benefit for the studied populations.</i></p> |

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| B2 | <p>Because these findings were not seriously considered in your coverage review, I would like to call your attention to a few of these publications noted below. <i>(see References Provided by Commenters below)</i></p> | <p><i>The PROTECT II study was reviewed in the coverage guidance. The manuscript by Maini et al. is a non-comparative consecutive case series from the USPELLA registry. The use of Impella 5.0 for post-pericardiotomy support was outside the scope of this coverage guidance. The manuscript by Flaherty et al. is a single-center retrospective cohort study; it should be noted that in the PROTECT II study, the rate of acute renal dysfunction did not vary between the Impella and IABP groups.</i></p> |
| B3 | <p>The Impella technology’s clinical benefits and safety data have been consistently demonstrated across studies and patient risk levels, and it is considered an important therapeutic option.</p> <p>Please consider revising your Impella coverage policy in light of this information.</p> | <p><i>Thank you for your comments.</i></p> |
| C1 | <p>I am an interventional cardiologist at the Oregon Heart and Vascular Institute, Sacred Heart Medical Center in Eugene/Springfield and have used Percutaneous Ventricular Assist Devices (pVADs) as an adjunct to both elective and urgent percutaneous coronary interventions (PCI) for those patients at high risk for surgery and for cardiogenic shock.</p> | <p><i>Thank you for your comments. HERC and its subcommittees value the input and experience of providers who use the interventions under review.</i></p> |
| C2 | <p>I have reviewed HERC’s coverage policy and was surprised on the Commission’s conclusion that pVADs are essentially as effective as IABPs, and each stand on equal footing in regard to net outcome. As such, the Commission jumps to the conclusion that for patients in need of hemodynamic support, <i>“The mechanism by which this is achieved (i.e., IABP or Impella) is unlikely to be important to patients. There is likely to be low variability in these values and preferences.”</i></p> | <p><i>The subcommittee believes that the comparative evidence for the use of Impella does not clearly support its benefit over IABP. Both of the references submitted by the commenter were included in the coverage guidance.</i></p> |

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| | <p>The Commission also writes <i>“Impella is extremely expensive and may be as much as 20 times more than an IABP.”</i></p> <p>I respectfully disagree with the justification behind this coverage policy. Not only is the Impella the only FDA approved therapy for both high-risk PCI and cardiogenic shock, there are numerous peer reviewed articles that pVADs such as the Impella improve health outcomes while reducing length of stay, repeat revascularizations, and readmissions.</p> | |
| C3 | <p>I would also like to take this opportunity to help answer questions on how the benefits of pVAD therapy exceed those of an IABP. Studies such as Protect II showed a significant reduction in adverse events at 90 days for Impella versus the IABP,¹ while ISAR-SHOCK demonstrated the Impella provided superior hemodynamic improvement compared with the IABP for cardiogenic shock patients.²</p> | <p><i>Both the PROTECT II study and the ISAR-SHOCK study were included in the coverage guidance. The reduction in major adverse events in PROTECT II were only apparent in the per-protocol analysis at 90-day follow-up and were driven mainly by a reduction in repeat revascularization, as noted in the coverage guidance. In addition to the fact that repeat revascularization was not part of the original composite outcome, the decision of whether to revascularize in an unblinded trial heightens the risk of bias. Hemodynamic outcomes were not selected as critical or important outcomes for the coverage guidance.</i></p> |
| C4 | <p>Moreover, only two (2) clinical practice guidelines were identified in the coverage policy, despite several other guidelines adopted by: Society for Cardiac Angiography and Interventions (SCAI), American College of Cardiology Foundation (ACCF), Heart Failure Society of America (HFSA), Society of Thoracic Surgeons (STS), the International Society for Heart & Lung Transplant (ISHLT), and Heart Rhythm Society (HRS).</p> | <p><i>The Clinical Expert Consensus statement from SCAI/ACCF/HFSA/STS was summarized in the coverage guidance.</i></p> <p><i>The 2013 ISHLT guideline has been added to the coverage guidance. We were unable to locate a relevant guideline from the Heart Rhythm Society, and no citation was provided.</i></p> |

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| C5 | A number of commercial payers provide coverage for the Impella when medically necessary, including, but not limited to: Aetna, United Healthcare, and Regence. | <i>The coverage policies of Aetna, Cigna, Moda, and Regence, as well as Washington Medicaid, are included in the coverage guidance in accordance with our usual methods.</i> |
| C6 | In conclusion, it is very concerning to me that this policy limits access for those patients covered under the Oregon Health Plan, placing patients that are otherwise surgically turned-down for their coronary artery disease or suffering from cardiogenic shock at a distinct disadvantage compared to the rest of the citizens of Oregon. | <i>Thank you for your comments.</i> |
| D1 | I have been a practicing interventional cardiologist for 27 years, 16 at Sacred Heart Medical Center. In my work, I frequently treat patients who are in shock from a heart attack or patients who would benefit from bypass surgery or coronary artery stents but are at extremely high risk of complications or mortality. | <i>Thank you for your comments.</i> |
| D2 | For many years, the only device available to support these patients has been the intra-aortic balloon pump. Although they are widely used, there is no good scientific evidence that balloon pumps actually improve patient outcomes. There have been several randomized clinical trials in patients with cardiogenic shock that have shown no clinical benefit. Because of this research, the guidelines published by the cardiology professional societies no longer recommend using a balloon pump routinely in this situation. | <i>We agree that the utility of IABP has been called into question. However, IABP was a comparator in all of the randomized controlled trials of Impella for ischemic cardiogenic shock, and Impella was not found to be superior to IABP</i> |
| D3 | More recently, the Impella assist device has become available. Unlike balloon pumps, Impella directly increases the amount of blood that is being sent to the rest of the body. The amount of support provided by the Impella is remarkable. When performing angioplasty in high-risk patients, it's not unusual for the heart to temporarily stop providing any meaningful blood flow. However, if an Impella is used, blood pressure and perfusion to the rest of the body are maintained. This allows time | <i>The subcommittee acknowledges that Impella devices may improve hemodynamic parameters, but those outcomes were not selected as important health outcomes for this review. EbGS discussed that if those hemodynamic parameters were significant enough to affect outcomes, then the results should have shown</i> |

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| | <p>for a better, more complete procedure to be done, and, frequently, is the only reason that the procedure can be performed at all.</p> <p>Unlike with the balloon pump, a number of studies have shown benefit to using Impella in high risk or severely ill patients. A community-wide initiative in Detroit has shown significant improvements in survival in patients with cardiogenic shock. A randomized study showed that high-risk patients undergoing coronary stenting had much better outcomes when supported with Impella compared to a balloon pump.</p> | <p><i>improved patient-oriented outcomes. The commenter did not submit references for the two studies mentioned here. The Detroit Cardiogenic Shock Initiative is a consecutive case series compared to historical controls and the interventions extended beyond use of temporary mechanical circulatory support. It was designed to establish the feasibility of early mechanical circulatory support. Our review of the PROTECT II trial data would not support the commenter's assertion that "high-risk patients undergoing coronary stenting had much better outcomes when supported with Impella compared to a balloon pump."</i></p> |
| D4 | <p>In my practice, we follow several patients who simply would not be alive today if they had not been treated with Impella. After decades of disappointing outcomes with balloon pumps, it's been a tremendous breakthrough to finally have a device that helps the sickest patients.</p> <p>In a time of tight health care budgets, we all must be careful stewards and use resources responsibly. Even though Impella is expensive, there is no other device that has been shown to improve outcomes in the relatively small group of patient in which it is being used. It's important to avoid creating a two-tier medical system, in which life-saving medical therapy is only available to patients with certain types of insurance.</p> <p>In general, the patients who receive the most benefit from bypass surgery and stenting are the sickest, but those are also the ones at highest risk from the procedures. Use of the Impella allows us to treat patients who otherwise would be at too high a risk. Without Impella, we would frequently have nothing to offer them.</p> | <p><i>Thank you for your comments. HERC and its subcommittees value the input and experience of providers who use the interventions under review, but must also weigh that experience against the outcomes of the published, peer-reviewed studies.</i></p> <p><i>The subcommittee had extensive discussion about the potential role of Impella to support PCI procedures that would not otherwise be offered or undertaken, as well as its value for patients who are not candidates for surgical revascularization. However, the subcommittee believed that the available randomized and comparative observational evidence did not establish that Impella support was superior to IABP.</i></p> |

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| | <p>The result would be even more expense for the health care system, with frequent and prolonged readmissions, referrals for permanent left ventricular assist devices and cardiac transplant, and death.</p> <p>It's likely that the result of denying coverage for Impella will be that the device will still be inserted, but only when all other options have been exhausted and have failed. Unfortunately, studies have shown that Impella is most effective when inserted early. If used as a last-ditch effort, the results are not nearly as positive. If the Impella is not reimbursed, hospitals will have to absorb the cost of the device, and patients will have worse outcomes.</p> <p>I urge you to reconsider your coverage decision so that beneficiaries of the Oregon Health Plan can receive the best, evidence-supported cardiac care.</p> | |
| E1 | <p>I am writing in regard to your coverage decision for the above-referenced policy. I am a thoracic and cardiac surgeon in Portland, Oregon and currently practice at both Portland Veterans Affairs Medical Center and Providence Portland Medical Center. I have supported a number of patients with either the Impella 5.0 or Impella LD in the setting of post-cardiotomy cardiogenic shock (PCCS).</p> <p>Historically, the overall mortality rate for PCCS is high, as much as 50-80%, despite advanced surgical techniques, inotropic support, and counterpulsation intra-aortic balloon pumps (IABPs). The Impella 5.0/Impella LD (left direct) are designed as minimally invasive and benefit the patient by providing circulatory support to restore normal cardiac function.</p> | <p><i>Thank you for your comments. HERC and its subcommittees value the input and experience of providers who use the interventions under review.</i></p> <p><i>However, the use of Impella 5.0 or Impella LD in the setting of post-pericardiotomy cardiogenic shock was beyond the scope of this coverage guidance, which was limited to percutaneously placed devices.</i></p> |
| E2 | <p>The RECOVER I study evaluated the safety and feasibility of Impella 5.0®/Impella LD® heart pumps in patients experiencing cardiogenic shock or low cardiac output syndrome following cardiac surgery. It concluded that the use of the Impella 5.0 is safe and feasible in patients presenting with PCCS, recovery of the native heart</p> | <p><i>See E1 above.</i></p> |

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| | <p>function was obtained in 93% of the patients discharged, and survival to 30 days, 3 months, and 1 year was 94%, 81%, and 75%, respectively.¹</p> <p>Moreover, Lemaire, et al. showed myocardial recovery was accomplished in most patients, and the 30-day, 90-day, and 1-year survival was 72.3%, 65.9%, and 63.8%, respectively.²</p> | |
| E3 | <p>I have performed almost forty procedures over the past twelve months, and have billed, and received payment for, the Impella heart pump procedure by Medicare and other major commercial payers. (I am also aware the hospital in which I perform the Impella procedure receives payment under the appropriate MS-DRG).</p> <p>This is because these payers recognize the cost benefit of this therapy while improving the survival rate in the setting of PCCS. Importantly, as a heart surgeon for high acuity patients, who helps lead a multidisciplinary team, this gives me an opportunity to meaningfully help patients that perhaps previously had no surgical option. These patients were then relegated to medical management of heart failure from surgical disease, that is doomed to failure.</p> <p>Please consider revising your Impella coverage policy in light of this information</p> | <p><i>The coverage policies of Aetna, Cigna, Moda, and Regence, as well as Washington Medicaid, are included in the coverage guidance in accordance with our usual methods.</i></p> |
| F1 | <p>I would like to provide my comments in regard to the Commission’s decision for non-coverage of the Impella device for any patient with Oregon Health Plan (OHP) as their medical insurance carrier.</p> | <p><i>Thank you for your comments.</i></p> |
| F2 | <p>I have used Impella for patients with severely reduced left ventricular systolic function and triple-vessel coronary artery disease, who have otherwise been turned-down for surgical revascularization given their comorbidities. While an IABP is known to provide counterpulsation therapy, randomized clinical trials have not shown hemodynamic or mortality benefit when compared with Impella.¹ Interventional cardiologists and cardiothoracic surgeons at Rogue Regional Medical Center rely on</p> | <p><i>Thank you for your comments. HERC and its subcommittees value the input and experience of providers who use the interventions under review.</i></p> <p><i>We agree that the utility of IABP has been called into question by large-scale trials. However, IABP was a</i></p> |

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| | <p>Impella support for providing percutaneous revascularization in individuals who are denied bypass surgery due to prohibitive surgical risk. This technology is lifesaving in these patients who otherwise have no other options available to them for revascularization.</p> | <p><i>comparator in all of the randomized controlled trials of Impella for ischemic cardiogenic shock.</i></p> <p><i>The subcommittee had extensive discussion about the potential role of Impella to support PCI procedures that would not otherwise be offered or undertaken and its value for patients who are not candidates for surgical revascularization. However, the subcommittee believed that the available randomized and comparative observational evidence did not establish that Impella support was superior to IABP for the studied populations.</i></p> |
| F3 | <p>As for cardiogenic shock, clinical outcomes remained poor prior to the availability of the Impella. Inotropes and vasopressors increase both contractility and overload, therefore increasing myocardial oxygen and mechanical work in an already compromised ventricle. Historically, the IABP is utilized in conjunction with an inotropic or vasopressor agent, but must be timed with precision to the patient's EKG to provide benefit. It is also not optimal in patients with tachycardia or heart rate irregularity. Studies have concluded no mortality benefit of IABP compared with medical therapy in the setting of AMI complicated by cardiogenic shock, and at 12 month follow-up of these patients, there no survival benefit observed between the IABP arm and control arm.² Major medical centers caring for shock patients increasingly rely on Impella support to provide effective hemodynamic support permitting patients sufficient time to recover myocardial function improving their chances of recovery and survival. We have personally seen multiple patients at Rogue Regional Medical Center who would not have survived had Impella support been unavailable to them.</p> | <p><i>The comparative evidence for the use of Impella in cardiogenic shock is quite limited (fewer than 100 patients) and does not clearly establish a benefit in this setting.</i></p> |

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| F4 | <p>In addition, the Commission’s evidence review is not consistent with the consensus of clinical experts familiar with the Impella technology. For instance, several guidelines were omitted from the draft coverage document, including those by the: Society for Cardiac Angiography and Interventions (SCAI), American College of Cardiology Foundation (ACCF), Heart Failure Society of America (HFSA), Society of Thoracic Surgeons (STS), the International Society for Heart & Lung Transplant (ISHLT), and Heart Rhythm Society (HRS).^{3,4,5}</p> | <p><i>The Clinical Expert Consensus statement from SCAI/ACCF/HFSA/STS was summarized in the coverage guidance.</i></p> <p><i>The 2013 ISHLT guideline has been added to the coverage guidance. We were unable to locate a relevant guideline from the Heart Rhythm Society, and no citation was provided.</i></p> |
| F5 | <p>Thank you for your time and reconsideration of the above-mentioned coverage policy. I strongly support the request that this life saving technology be made available to this group of patients.</p> | <p><i>Thank you for your comments.</i></p> |
| G1 | <p>Abiomed, Inc. appreciates the opportunity to comment on the HERC Draft Coverage Guidance for Temporary Percutaneous Mechanical Circulatory Support with Impella Devices. As the manufacturer of Impella, we would like to respond to comments raised at the September 6 meeting of the Evidence-based Guidelines Subcommittee and in the Draft Guidance with additional clinical data demonstrating Impella's clinical effectiveness in comparison to an Intra-Aortic Balloon Pump (IABP).</p> <ul style="list-style-type: none"> • Impella is the only FDA PMA approved device proven safe and effective for Protected PCI and Cardiogenic Shock • Seven clinical society guidelines support the use of Impella in severely ill patient populations who have no other option for care | <p><i>Thank you for your comments.</i></p> |
| G2 | <p>The Draft Guidance does not reflect the published peer reviewed evidence and consensus clinical society guidelines, and would limit Oregon Health Plan beneficiaries' access to the only FDA approved medical device for cardiogenic shock.</p> | <p><i>Clinical society guidelines are considered as contextual information for every HERC coverage guidance. The most recent (2015) Expert Consensus Statement of SCAI/ACC/HFSA/STS was included in the coverage</i></p> |

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| | <p>We respectfully request that the HERC finalize Coverage Guidance consistent with the clinical society guidelines or withdraw the Draft Guidance.</p> <p><u>Impella Is A Well Validated Technology Supported By Consensus Clinical Guidelines</u></p> <p>Impella is the only FDA approved, PMA on-label therapy for patients with high risk PCI (HR-PCI) and cardiogenic shock (CGS). Impella heart pumps have the ability to stabilize a patient's hemodynamics, perfuse end organs, and allow for recovery of the native heart. Impella can be used as a bridge for many critically ill cardiac patients.¹⁻⁸</p> <p>Impella is recognized as the clinical standard for HR-PCI and CGS. In total, seven clinical society guidelines support the use of Impella in these severely ill patient populations.⁹⁻¹⁵</p> <p>In comparison to Impella, an IABP provides limited flow augmentation with more heart dysfunction and has shown risk of stroke with no improvement in hemodynamics or mortality in CGS. As a result, the American Heart Association has downgraded IABP from a Class I recommendation to Class IIB in its guidelines on hemodynamic support in post-MI CGS. Additionally, the 2015 SCAVACC/HFSA/STS clinical expert consensus statement on the use of percutaneous mechanical circulatory support devices in cardiovascular care states: <i>“In the setting of profound cardiogenic shock, IABP is less likely to provide benefit than continuous flow pumps including the Impella CP...”</i>¹⁶</p> <p>Reflecting this clinical consensus, any other government and commercial payers cover Impella for HR-PCI and CGS including Regence, United Healthcare, Aetna, Cigna, Humana, and Highmark. Multiple Medicare Administrator Contractors provide coverage policies for pVADs (including Impella). Moreover, no Medicare contractors non-cover Impella. Internationally, the Canadian Association of Interventional</p> | <p><i>guidance, as was the older AHA/ACCF guideline on the management of STEMI.</i></p> <p><i>The coverage policies of Aetna, Cigna, Moda, and Regence, as well as Washington Medicaid, are included in the coverage guidance in accordance with our usual methods.</i></p> <p><i>The overall results of the PROTECT II study, including the 90-day per-protocol findings, were reviewed in the coverage guidance. The subgroup findings by use of rotational atherectomy were not included in the initial report of this trial. Although this was a pre-specified subgroup analysis, in an unblinded trial like PROTECT II, the decision to use rotational atherectomy itself may have been influenced by the treatment allocation (i.e., Impella vs. IABP), which limits any conclusions regarding subgroup effects. The authors acknowledged this limitation: “Our study is limited by the nonrandomized comparison between nonatherectomy PCI, by the constraints of its open-label design, and by its small sample size. The nonblinded design of the study most likely increased operator bias in selecting rotational atherectomy and influenced the manner in which it was performed.”</i></p> <p><i>The ISAR-SHOCK trial was also included in the coverage guidance. The hemodynamic improvements observed in</i></p> |

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| | <p>Cardiology as well as government agencies in Germany, the United Kingdom, Japan and almost all other modern healthcare agencies provide coverage for Impella.</p> <p><u>Peer Reviewed Publications Support Coverage for Impella</u></p> <p>Multiple peer reviewed publications demonstrate that Impella optimizes conditions for native heart recovery and reduces major adverse events and repeat revascularizations.</p> <p>The PROTECT II study was a prospective, multi-center, randomized, open label, active controlled clinical study to assess the safety and efficacy of the Impella 2.5 System compared to IABP.¹⁷ At the 90-day study exit follow-up, there was an average 22% relative increase in LVEF from baseline and a 58% improvement in NYHA functional class III/IV. Within the (pre-specified) ITT population not treated with atherectomy, the Impella 2.5 patients had better outcomes compared to those who received an IABP, with a significant 25% relative risk reduction in MAE incidence at 90 days.</p> <p>The ISAR-SHOCK study showed a significant improvement of cardiac index in the Impella 2.5 arm compared to the IABP arm post-device insertion.¹⁸ After 24 hours of support, fewer patients supported with the Impella 2.5 required inotropes compared to patients supported with an IABP.</p> <p>Although we recognize the value of prospective randomized control trials to assess medical devices, real world evidence through observational patient registries provides additional validation of the benefits to this severely ill patient population. A recent registry demonstrated that modifiable treatment patterns are associated with higher survival when Impella is used.</p> <p>The attached appendix lists peer-reviewed publications supporting the use of Impella.</p> | <p><i>that trial did not correspond with selected outcomes for this coverage guidance.</i></p> <p><i>HERC methods rely on systematic reviews and randomized controlled trials. Observational studies, particularly non-comparative observational studies, are given lower weight, especially when RCT data exist.</i></p> |

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| G3 | <p><u>Health Quality Ontario Assessment has limited reliability</u></p> <p>The Draft Guidance relies heavily on the Health Quality Ontario "Percutaneous Ventricular Assist Devices: A Health Technology Assessment." We have previously shared our concerns about the methodology of this assessment with HQO, and, as noted above, the HQO assessment contradicts the Canadian Association of Interventional Cardiology. We requested that the report searchable on PubMed be removed until methodological errors are corrected.</p> <p>The HQO Report includes serious methodological flaws and is not peer-reviewed. First, the review selectively removes positive efficacy studies, removes or has inconsistent use of studies' own conclusions, and does not follow PRISM compliant protocols. Second, the committee did not seek advice from physicians with extensive Impella experience to identify appropriate clinical use in HR- PCI and CGS. Lastly, the cost model is based on unique and unvalidated assumptions, adverse events not assessed in the trials referenced, and cost levels from other countries omitted.</p> <p>As a result, there is a significant difference in efficacy data in the HQO Report compared to data from other government agencies and clinical societies. In comparison to the extensive efficacy data from peer-reviewed studies in the United States, the HQO report must be weighed in context and should not be the basis for the coverage guidance.</p> | <p><i>The HQO review is presented as one line of systematically reviewed evidence in the coverage guidance, but other lines of evidence are also included. In addition, because of the incomplete overlap in the included reviews' analysis of comparative studies, we separately summarized the results of those studies in the data table.</i></p> <p><i>That said, we believe that the search strategy outlined in Appendix 1 of the HQO report was comprehensive and that the pre-specified inclusion and exclusion criteria they outlined were clear and fairly applied. A PRISMA flow diagram is on page 15 of the HQO report.</i></p> <p><i>The subcommittee did not consider the economic analysis performed by HQO in their deliberations.</i></p> |
| G4 | <p><u>Draft Guidance Undervalues the Cost-Effectiveness Of Impella</u></p> <p>The Draft Guidance's cost-effectiveness analysis underestimates Impella's clinical benefits and overstates its costs by failing to consider the costs of other treatments and their complications. For example, the Draft Guidance suggests that Impella does not reduce MACCE, but the largest randomized controlled trial in setting of HR-PCI demonstrated a statistical difference in MACCE.²⁰⁻²¹ Impella has also proven cost</p> | <p><i>The draft coverage guidance did not seek to undertake a cost-effectiveness analysis, and HERC generally does not consider economic analyses when the supporting evidence is not judged to be sufficient to inform such analyses. In this case, the only statistically significant benefit addressing an outcome of interest in the RCTs</i></p> |

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| | <p>effective through reduction in complications, length of hospital stay, re- admissions, and overall costs compared with IABPs and other alternative treatments.²² The Draft Guidance does not account for the total costs of IABPs or other alternative treatments.</p> | <p><i>was for the composite outcome of major adverse events in the per-protocol analysis of PROTECT II. We are not aware of a cost-effectiveness model that is able to capture the economic effects of such a composite outcome.</i></p> <p><i>The reference cited here to establish a reduction in MACCE in the PROTECT II trial relies on a post-hoc analysis using a revised definition of periprocedural myocardial infarction in place of the definition used in the original protocol. Such an analysis should be regarded as exploratory rather than definitive.</i></p> |
| G5 | <p>Abiomed appreciates the opportunity to provide written comments, and welcomes the opportunity to provide a detailed presentation about the clinical benefits of Impella in person at the next public meeting.</p> | <p><i>Thank you for your comments.</i></p> |
| H1 | <p>I would like to submit my comments in regard to OHP’s current policy for the <i>Temporary Percutaneous Mechanical Circulatory Support with Impella Devices</i>. As an interventional cardiologist serving the patients of OHP, it is concerning to me that this subset of patients will not be provided access to the only FDA approved therapy for high risk PCI or Cardiogenic Shock.</p> | <p><i>Thank you for your comments.</i></p> |
| H2 | <p>Except for its’ cost, the current policy concludes the Impella and the intra-aortic balloon pump (IABP) can be used interchangeably, “...Impella appears to offer no benefit over the current standard of care at a much greater cost.”</p> <p>The Commission theorizes, “Impella is much more expensive than the comparator, and patient values and preferences would not lean toward either direction.”</p> | <p><i>We believe that the available comparative evidence does not support a conclusion that Impella is superior to IABP for the patients and outcomes considered in the scope of the coverage guidance.</i></p> <p><i>The Stretch et al. manuscript referenced here is a non-comparative cross-sectional study of patients receiving</i></p> |

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| | <p>To explain, patients who receive active LV unloading by the Impella are more hemodynamically stable and allows for complete revascularization, which helps avoid unplanned, repeat, PCI or surgical interventions, ultimately adding costs and increased risk for complications (examples include stroke, death, and MI) in a future healthcare encounter. In the emergent setting, Stretch et al. (2014) showed that IABP increased cost and mortality, while pVADs including Impella decreased both in PCI patients and specifically in AMI cardiogenic shock.¹</p> | <p><i>mechanical circulatory support in the Nationwide Inpatient Sample. It essentially describes trends in the use of mechanical circulatory support between 2007 and 2011 and includes devices other than Impella. This report was not intended to compare IABP and Impella, and indeed the authors noted that even after adjusting for all other variables in their analysis, later calendar years were predictive of lower mortality, suggesting a secular temporal trend toward improved outcomes.</i></p> |
| H3 | <p>Therefore, I would request the Commission reconsider its policy against Impella by evaluating the cost-effectiveness and long-term outcomes of Impella therapy versus the IABP, as opposed to the upfront costs within a single healthcare encounter.</p> | <p><i>Thank you for your comments.</i></p> |

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