Health Evidence Review Commission's Value-based Benefits Subcommittee

November 9, 2023

8:00 AM - 1:00 PM

Clackamas Community College
Wilsonville Training Center, Room 112 (limited seating)
29373 SW Town Center Loop E, Wilsonville, Oregon, 97070

Join online meeting here

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Section 1.0

Call to Order

Agenda
Value-based Benefits Subcommittee (VbBS)
November 9, 2023

8:00 am–1:00pm

Online & Clackamas Community College (Limited seating)

Wilsonville Training Center, Room 112

29373 SW Town Center Loop E

Wilsonville, Oregon 97070

All agenda items are subject to change and times listed are approximate.

Public comment will be taken on each topic per HERC policy at the time at which that topic is discussed.

	Time	Topic
I.	8:00 AM	**Call to Order, Roll Call, Approval of Minutes**
II.	8:05 AM	**Staff report**
III.	8:15 AM	**Straightforward/Consent Agenda** 1) Straightforward consent table 2) Straightforward CGM code clean up 3) Straightforward guideline updates -NCCN reference updates -Preventive services guideline date updates
IV	8:20 AM	**Advisory panel reports** A. Oral Health Advisory Panel (OHAP) report 1. 2024 CDT code placements 2. Dentures, crowns and dental implants *(Certain dental coverage issues)* 3. OHAP straightforward guideline note change B. Behavioral Health Advisory Panel (BHAP) report 1. BHAP straightforward code change recommendation 2. 2024 HCPCS codes related to behavioral health

	Time	Topic
		3. Problems related to unspecified psychosocial circumstances *(An issue linked to a social or emotional situation that isn't described in more detail)* 4. Transcranial magnetic electrical stimulation guideline update *(TMS uses magnets to create a strong, targeted electric current in certain parts of the brain. which may help improve mental health conditions including depression)* C. Genetics advisory panel report *1.* Revisions to the hereditary cancer genetic testing guideline *(Changes to the guideline on medical testing that helps determine a higher risk of developing certain types of cancer due to their family's genetic history)* 2. Genetic testing for intellectual disabilities, developmental disabilities and autism spectrum disorders *(Gene testing to see if genes play a role in why someone has problems with thinking, growing, or a certain kind of behavior)* 3. 2024 CPT codes related to genetic testing and edits to the new next generation sequencing of cancer guideline 4. Updates the references to the American College of Medical Genetics (ACMG) in the non-prenatal genetic testing guideline New discussion item related to genetic testing 5. OncoExTra *(Gene testing for advanced cancer)*
V	10:00 AM	**New discussion items** • Computer assisted navigational bronchoscopy (*Using computer pictures to help guide where a doctor looks in the lungs to get sample tissue)*
VI.	10:30 AM	**2024 CPT Code Review** 1. Straightforward 2. Anterior thoracic vertebral body tethering *(Attaching a device to the bones of the spine to treat abnormal curves of the spine)* 3. Posterior nasal nerve ablation *(Destroying the nerve that causes the nose to make mucous)* 4. Phrenic nerve stimulator *(A device to help a person who is using a breathing machine to breathe better)* 5. Urethral stricture dilation with drug-coated balloon catheter *(A device to widen a narrowing of the tube that drains urine from the bladder)*

	Time	Topic
		6. Transcervical ablation of uterine fibroids *(A procedure to destroy noncancer growths in the uterus)* 7. Suprachoroidal injection *(A way to deliver medication to the back of the eye)* 8. Enhanced Liver Fibrosis (ELF) test *(A test to check on the health of the liver)* 9. Coronary lithotripsy *(A procedure to help open blocked blood vessels to the heart)* 10. HIPEC (Hyperthermic (or Heated) Intraperitoneal Chemotherapy (HIPEC)) *(A treatment for advanced cancer)* 11. Low-level laser therapy *(Using weak lasers to help protect the lining of the mouth during cancer treatment or after surgery* 12. Caregiver training *(Teaching a caregiver to help a patient with activities of daily living)* 13. Pelvic examination *(Extra charge for practice overhead)* **2024 HCPCS Code Review** **2024 PLA Code Review** 1) Lipoprotein profile *(A blood test for fats and proteins)* *2)* Drug metabolism codes *(Tests to show how drugs are processed and broken down in the body)* 3) Maternal serum biomarkers for prediction of preeclampsia *(Blood tests to predict a serious condition for pregnant people)* *4)* Pre-implantation genetic testing *(Genetic testing before infertility treatment for people who have trouble having babies)* 5) Omnia COVID test *(A test for the COVID-19 virus)*
VII.	11:15 AM	**Previous discussion items** A. Breast reduction for macromastia *(Liver tumors that started out in some other part of the body)* *B.* Standard of care identification for gender affirming treatment C. Tobacco cessation guidelines *(Requiring patients to stop tobacco use prior to several surgeries)*
VIII.	11:30 AM	**New discussion items** A. Tabled from September a. PSMA PET scans for prostate cancer *(Screening for prostate cancer)* i. Related HCPCS code C9156

	Time	Topic
		b. Cardiac resynchronization therapy *(Pacemaker and heart defibrillator placement for heart failure)* c. Nasal fracture repair *(Treatments for broken noses)* d. Treatment of liver metastases *(Liver tumors that started out in some other part of the body)* B. Early packet a. Listening session topics: i. Foot and nail care for high-risk patients in facilities *(Nail and foot care for people who live in nursing homes)* b. Central auditory processing disorder testing *(Tests for a condition making it hard for a hearing person to understand sounds, even if their ears work correctly)* c. Instrument based ocular screening *(A way to check a child's vision using a special camera instead of an eye chart)* C. Severe exfoliating skin conditions *(Severe shedding of the skin that can affect overall health)* D. Refugee screening *(Medical screenings for people arriving from other countries who are seeking safety and protection from war or other dangers)*
XI.	12:55 PM	**Public comment on topics not on the agenda**
XII.	1:00 PM	**Adjournment**

Value-based Benefits Subcommittee (VbBS) Summary

For Presentation to:
Health Evidence Review Commission on September 28, 2023

For specific coding recommendations and guideline wording, please see the text of the September 28, 2023, VbBS minutes.

Recommended Code Movement (Changes to the 1/1/2024 Prioritized List unless otherwise noted):

- Add new HCPCS codes to various funded and unfunded lines
- Add the procedure codes for insertion of endobronchial valves to a funded line
- Add the procedure codes for topical oxygen therapy to guideline note 173 and Line 662
- Add the procedure codes for screening and diagnostic CT colonography to funded lines or files
- Add the diagnosis codes for various types of ichthyosis to a funded line
- Add the diagnosis code for FoundationOne CDx tumor testing to the diagnostic procedure file
- Add the procedure codes for percutaneous electrical nerve stimulation and neuromodulation for IBS to an unfunded line
- Add procedure codes for continuous glucose monitors to two funded lines
- Make various straightforward coding changes

Item Considered but No Recommendations for Changes Made:

- MILD procedure for low back pain

Recommended Guideline Changes (Changes to the 1/1/24 Prioritized List unless otherwise noted):

- Add a new guideline for endobronchial valves
- Edit the PANDAS/PANS guideline to add additional examples of provider types
- Add a new guideline for diagnostic CT colonography
- Edit the preventive services guideline to correct the reference to the OHA vaccine program and to outline limited coverage for screening CT colonography
- Add a new guideline for next generation sequencing testing of cancer tissue
- Delete the GnRH analog guideline
- Edit the deep brain stimulation for refractory epilepsy guideline to reduce the number of required medication trials
- Edit the continuous glucose monitoring guideline to include coverage criteria for type 2 diabetes and gestational diabetes

Minutes
Value-based Benefits Subcommittee (VbBS)

Online and Clackamas Community College, Wilsonville OR
September 28, 2023

Members Present: Holly Jo Hodges, MD, MBA, Chair; Brian Duty, MD, Vice-Chair; Cris Pinzon, MPH, RN; Kathryn Schabel, MD; Mike Collins; Adriane Irwin, PharmD.

Members Absent: Kevin Olson, MD; David Saenger, MD.

Staff Present: Ariel Smits, MD, MPH; Amy Cantor, MD, MPH; Jason Gingerich; Liz Walker, PhD, MPH; Daphne Peck.

Also Attending: Shauna Durbin, Rachel McCausland, Ronnie Johnston, Val King, MD, MPH & Marcus Bachhuber (Center for Evidence-based Policy); Dawn Mautner, MD; Jason Daniels (OHA); Rebecca Gale; Lawrence Lyon, MD; Ashlynn Wilson; Deb Brugman; Rafat Fields (Abbott Diabetes Care); Jennifer Olson; Stephanie A; Taylor Sibley; Mariham Fahim; Laura; Carissa Kemp (American Diabetes Association); Diana; Dr. Matthew Garoufalis; Dr. Dave Griffin; Stacy Reel; Edward Ysunza; Kyle Dickey; Marie Frazzitta; Kacie Frederick; Thomas Grace, MD; Linda Nunes; Sharon McDowell; Laura Lacey; Melissa; Joseph El Youssef; Roger Citron (DURM Director); DT; Renee Taylor; Brian Wilhelmsen; Kelsie; Kyle Dickey; Stephanie A; Katie (Performance Home Medical); Kelsie, Sarah Like.

Call to Order, Minutes Approval, Staff Report

The meeting was called to order at 8:30 am and roll was called. A quorum of members was present at the meeting. Minutes from the August 17, 2023, VbBS meeting were reviewed and approved with no modifications.

Jason Gingerich gave the orientation statement and staff report. Daphne Peck has moved into a new role as the community outreach coordinator for HERC. A new employee will take over communications with members and meeting coordination. Membership updates were given. Dr. Larry Lyon was introduced, who will be joining HERC as a new member beginning at the November meeting. Gingerich announced that there is an open recruitment for an insurance representative for HERC, and other open positions on subcommittees.

Liz Walker gave an update on rulemaking. New HERC rules will be placed on the secretary of state bulletin and public comments are welcome beginning October 1.

Straightforward/Consent Agenda

Discussion: There was no discussion about the consent agenda items, other than the placement of the Moderna RSV vaccine. A member stated that there is no vaccine that is FDA approved that used that CPT code (90683) and therefore the code was best placed on the Excluded file rather than the Ancillary file.

Recommended Actions:

1) Add 11920-11922 (Tattooing, intradermal introduction of insoluble opaque pigments to correct color defects of skin, including micropigmentation) to line 191 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER
2) Modify GN221 as shown in Appendix A
3) Delete GN93
4) Modify GN106 as shown in Appendix A
5) Add CPT 90480 and 91318-91322 (COVID vaccine administration) to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
6) Delete from line 3: CPT 91302, 91303, 91310, 91312, 91313, 91314, 91315, 91316, and 91317
    a. Recommend HSD place these CPT codes on the EXCLUDED FILE
7) Add CPT 90380 and 90381 (Respiratory syncytial virus, monoclonal antibody) and 90679 (Respiratory syncytial virus vaccine, preF, recombinant, subunit, adjuvanted, for intramuscular use) to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
8) Advise HSD to place CPT 90683 (Respiratory syncytial virus vaccine, mRNA lipid nanoparticles, for intramuscular use) on the Excluded file

MOTION: To approve the recommendations as modified. CARRIES 6-0.

MILD procedure for low back pain

Discussion: Smits presented the meeting materials. There was no discussion about the staff recommendation to continue non-coverage.

Recommended Actions:

1) Modify GN173 as shown in Appendix A

MOTION: To approve the recommendations as presented. CARRIES 6-0.

October 2023 HCPCS codes

Discussion: Smits noted that one code was a straightforward placement, and 2 codes were referred to BHAP for discussion. The remainder of the codes were recommended for non-coverage. There was minimal discussion.

Recommended Actions:

1) Add HCPCS C9789 (Instillation of anti-neoplastic pharmacologic/biologic agent into renal pelvis, any method, including all imaging guidance, including volumetric measurement if performed) to 214 CANCER OF KIDNEY AND OTHER URINARY ORGANS
2) Add the HCPCS codes below to line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS and modify GN173 as shown in Appendix A
    a. A9268 Programmer for transient, orally ingested capsule
    b. A9269 Programable, transient, orally ingested capsule, for use with external programmer, per month
    c. A9292: Prescription digital visual therapy, software-only, FDA cleared, per course of treatment
    d. C9788 Opto-acoustic imaging, breast (including axilla when performed), unilateral, with image documentation, analysis and report, obtained with ultrasound examination
    e. C9790 Histotripsy (i.e., non-thermal ablation via acoustic energy delivery) of malignant renal tissue, including image guidance
    f. C9791 Magnetic resonance imaging with inhaled hyperpolarized xenon-129 contrast agent, chest, including preparation and administration of agent
    g. E0490: Power source and control electronics unit for oral device/appliance for neuromuscular electrical stimulation of the tongue muscle, controlled by hardware remote
    h. E0491: Oral device/appliance for neuromuscular electrical stimulation of the tongue muscle, used in conjunction with the power source and control electronics unit, controlled by hardware remote, 90-day supply
    i. K1028: Power source and control electronics unit for oral device/appliance for neuromuscular electrical stimulation of the tongue muscle for the reduction of snoring and obstructive sleep apnea, controlled by phone application
    j. K1029 Oral device/appliance for neuromuscular electrical stimulation of the tongue muscle, used in conjunction with the power source and control electronics unit, controlled by phone application, 90-day supply

MOTION: To approve the recommendations as presented. CARRIES 6-0.

Breast reduction for macromastia

Discussion: The group desired that there be clear coverage for women with symptomatic macromastia, who have neck, back or shoulder pain, or severe intertrigo. There was concern

about adding the codes from the current macromastia line to only the back line as shoulder pain and intertrigo. The group wanted the ICD-10-CM and CPT codes from the macromastia line added to the shoulder pain line as well as the intertrigo line. It was noted that intertrigo was on an unfunded line (line 503). The group requested that severe intertrigo be added to the severe inflammatory skin disease line where it would be funded if it met guideline note criteria. The inflammatory skin disease line would then have the macromastia codes. As part of the 2026 Biennial Review (which starts in January 2024), the macromastia line would be changed to "symptomatic macromastia" and reprioritized and the duplicative coding deleted. Asymptomatic macromastia would then be included on the line for musculoskeletal conditions with no treatment required line.

Staff will work on operationalizing the requested changes and bring back the final guideline wording to the November VBBS meeting. Staff will also present the VBBS intent to HERC at their meeting on September 28th and include any HERC input in this finalization process.

Endobronchial valves

Discussion: Smits reviewed the summary document. There was some discussion about adding a criterion in the new guideline that patients should not be lung volume reduction surgery candidates; however, the group decided against that as this procedure is less invasive and should be an option available to patients who might not wish an open surgery. The group unanimously elected to approve option 2.

Recommended Actions:

1) Add CPT 31647-31649 and 31651 (bronchoscopy with insertion or removal of bronchial valve(s)) to line 283 CHRONIC OBSTRUCTIVE PULMONARY DISEASE; CHRONIC RESPIRATORY FAILURE and remove these codes from line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
    a. 31647 Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with balloon occlusion, when performed, assessment of air leak, airway sizing, and insertion of bronchial valve(s), initial lobe
    b. 31648 Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with removal of bronchial valve(s), initial lobe
    c. 31649 Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with removal of bronchial valve(s), each additional lobe
    d. 31651 Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with balloon occlusion, when performed, assessment of air leak, airway sizing, and insertion of bronchial valve(s), each additional lobe
2) Delete the entry for endobronchial valves from GN173 as shown in Appendix A
3) Add a new guideline to line 283 as shown in Appendix B

MOTION: To approve the recommendations as presented. CARRIES 6-0.

Topical oxygen therapy

Discussion: Smits reviewed the summary document. It was noted that the included studies were limited to intermediate outcomes such as wound healing, rather than critical outcomes such as amputation rates. Pinzon was interested this technology as another tool in the diabetic foot ulcer treatment tool kit.

Public Testimony:

Matthew Garoufalis, an Illinois podiatrist who is the CMO of AOTI (a manufacturer of a topical oxygen device) and past president of the American Podiatry Association testified about his use of this technology on hundreds of patients. He referred to the Yellin 2021 real world study that showed reduced hospitalizations and decreased amputation rate with TOT.

Dave Griffin, a non-Oregon community podiatrist, testified that TOT can address access issues, particularly transportation issues. He testified that black and brown patients frequently lack transportation and access to care and experience a higher rate of diabetes and diabetic foot ulcers. He noted the high mortality from diabetic foot ulcers, and the high cost of care for this condition. TOT is done in the home and is high quality care. Schabel asked him how TOT could impact equity. Griffin responded that TOT is used at home and addressed transportation needs. Pinzon asked if this technology could be used with the houseless population. Griffin answered no, as it requires electricity.

Edward Ysunza, the chief podiatrist at the Portland VA testified about the VA experience with TOT for the past 2 years. He noted that the VA has found very good results in patients who fail usual care. He noted that studies have shown fewer hospitalizations, amputations, and ulcer recurrence. It helps patients be more involved in their own care. Pinzon asked about how generalizable the VA population is to the Medicaid population. Ysunza responded that Oregon VA patients are similar to the general Oregon population.

The subcommittee discussed that TOT was more accessible and would benefit patients with transportation issues. There was a discussion that if a subpopulation that could benefit most from TOT could be identified, then coverage might be considered for that group. Schabel noted that the studies that should be done would compare TOT to no therapy (reflecting the population with little access to care). Irwin and Collins felt that the data does not support that TOT will actually meet the needs of any population, marginalized or not. The decision was to approve the staff recommendation. HERC staff were directed to monitor the CMS review of TOT and bring this topic back for reconsideration if CMS decides to add coverage for TOT.

Recommended Actions:

1) Add topical oxygen therapy to line 662/GN173 as shown in Appendix A
    a. A4575 Topical hyperbaric oxygen chamber, disposable
    b. E0446 Topical oxygen delivery system, not otherwise specified, includes all supplies and accessories

MOTION: To approve the recommendations as presented. CARRIES 5-1 (Schabel nay).

Edits to the PANDAS/PANS guideline

Discussion: Love requested that the term "naturopath" be changed to "naturopathic physician" in the guideline. There was no other discussion and staff recommendations with the modification to the reference to naturopathic physicians was approved.

Recommended Actions:

1) Modify guideline note 228 as shown in Appendix A

MOTION: To approve the recommendations as modified. CARRIES 6-0.

CT colonography

Discussion: Smits presented the staff summary. There was discussion regarding including patients on anti-coagulation that could not be bridged for colonoscopy as an eligible group for CT colonography. There was concern from some members that such patients might not be able to have a polyp removed or a cancer treated if found. The decision was made to not include this population and accept the staff recommendation as presented.

Recommended Actions:

2) Advise HSD to add CPT 74261-74262 (Computed tomographic (CT) colonography, diagnostic, including image postprocessing; with/without contrast material) to the Diagnostic Procedures File
3) Remove CPT 74261-74262 from line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS and delete the entry in GN173
4) Add a new Diagnostic guideline as shown in Appendix B
5) Delete CPT 74263 (Computed tomographic (CT) colonography, screening, including image postprocessing) from line 502 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS and from the GN172 entry as shown below and add to line 3 PREVENTIVE SERVICES WITH EVIDENCE OF EFFECTIVENESS
6) Modify GN106 as shown in Appendix A

MOTION: To approve the recommendations as presented. CARRIES 6-0.

PSMA PET for prostate cancer

Discussion: Tabled to November 2023

Cardiac resynchronization therapy

Discussion: Tabled to November 2023

Ichthyosis

Discussion: There was minimal discussion on this topic.

Recommended Actions:

1) Add the following ICD-10-CM codes to line 426 SEVERE INFLAMMATORY SKIN DISEASE effective 1/1/2024
    a. Q80.0 Ichthyosis vulgaris
    b. Q80.1 X-linked ichthyosis
    c. Q80.2 Lamellar ichthyosis
    d. Q80.3 Congenital bullous ichthyosiform erythroderma
    e. Q80.4 Harlequin fetus
    f. Q80.8 Other congenital ichthyosis
    g. Q80.9 Congenital ichthyosis, unspecified
2) Strike through line 539 ICHTHYOSIS effective 1/1/2024

~~**Line: 539**~~
~~Condition:ICHTHYOSIS~~
~~Treatment:MEDICAL THERAPY~~
~~ICD-10:Q80.0-Q80.9~~
~~CPT:98966-98972,99051,99060,99070,99078,99202-99215,99281-99285,99341-99359,99366,99374,99375,99381-99404,99411-99417,99421-99449,99451,99452,99487-99491,99495-99498,99605-99607~~
~~HCPCS:G0068,G0071,G0088,G0090,G0248-G0250,G0318,G0323,G0425-G0427,G0463,G0466,G0467,G0490,G0511,G2012,G2211,G2212,G2214,G2251-G3003~~

3) Delete line 539 ICHTHYOSIS effective 1/1/2026
4) Modify guideline note 21 as shown in Appendix A

MOTION: To approve the recommendations as presented. CARRIES 5-0 (Duty absent).

FoundationOne CDx

Discussion: Smits reviewed the summary document. There was minimal discussion, other than defining "adequate functional status" as having an ECOG (Eastern Cooperative Oncology Group Performance Status) score of 0-2.

Public testimony
Deb Brugman from FoundationOne and a genetic counselor by training, noted that 16 Medicaid programs cover the FoundationOne CDx test. She noted that the proposed guideline criteria were in line with Medicare guidelines and expert guidelines.

Recommended Actions:

1) Advise HSD to move PLA 0037U (FoundationOne CDx) from the Excluded file to the Diagnostic Procedure File
2) Adopt a new diagnostic guideline as shown in Appendix B

MOTION: To approve the recommendations as presented. CARRIES 6-0.

Nasal fracture repair

Discussion: Tabled to November 2023

Treatment of liver metastases

Discussion: Tabled to November 2023

Percutaneous electrical nerve stimulation and neuromodulation for IBS

Discussion: There was minimal discussion on this topic.

Recommended Actions:

1) Modify guideline note 173 as shown in Appendix A

MOTION: To approve the recommendations as presented. CARRIES 5-0 (Duty absent).

Coverage guidance: continue glucose monitoring

Discussion: King presented the evidence summary for the draft coverage guidance report. Cantor reviewed the summary document, including the proposed changes to the current guideline note for continuous glucose monitoring.

Hodges stated support for coverage of CGMs that are therapeutic, since non-therapeutic devices do not replace finger sticks and do not allow for clinical decision-making. She asked for clarification of criteria for CGM re-initiation. Roger Citron (OHA P&T) described the prior authorization (PA) process and considerations for how often people will need sensors, a transmitter and receiver. He said when PA comes up for renewal, documentation would be needed from the provider attesting to use. He said PA can be initially lax and become more restrictive if non-use was evident. Hodges and Citron discussed initial PA periods, given an expectation of a follow-up visit within 3-6 months with the patient and prescriber. This clause was added to criterion (B) of the guideline note. Pinzon asked about replacement of lost CGM items and how that would affect the PA process. Citron said that PA pharmacy requests are responded to within 24 hours so there should not be a delay in filling prescriptions but that the DME process may be different. Pinzon asked King about the MOBILE trial and how the recommendation came to require multiple daily insulin doses. King said that MOBILE study participants were a mix of intermediate-acting and basal insulin regimens, and it was EbGS's recommendation to require multiple doses given the low confidence of the evidence. Pinzon expressed surprise that the longest follow-up available of the studies was 24 weeks, given that this is a chronic condition which is very common. King said EbGS members expressed similar sentiments.

Public testimony

Thomas Grace, Illinois-based provider employed by Dexcom (CGM manufacturer): Grace testified about the MOBILE study and the heterogeneity of insulin regimens given the basal dose. He stated that people with diabetes who use insulin often fear becoming hypoglycemic and that CGM use can prevent hypoglycemia. He said there is a lot of real-world evidence and that other metrics besides HbA1c exist to measure blood sugar. He advocated for coverage of CGM even for patients with HbA1c levels lower than 8.0, who didn't meet the other criteria for coverage.

Carissa Kemp, Idaho-based Director of State Government Affairs of the American Diabetes Association: Kemp said that the ADA is excited to see the draft recommendation expanding the eligible CGM population but has concerns about the multiple daily dose requirement. Kemp said that Medicare recently changed its requirement to any insulin use and asked that the subcommittee align with this recommendation. She asked for the subcommittee to remove the HbA1c criterion from being one of the possible pathways for obtaining CGM. She also stated that CGM can achieve cost savings. She said that many people with diabetes do not have access to technologies such as CGM compared to higher income peers and that this is a health equity issue.

Mariham Fahim, non-Oregon provider employed by Abbott Diabetes Care (CGM manufacturer): Fahim thanked the subcommittee for considering this expansion but asked the subcommittee to further expand the population by removing the multiple daily dose requirement. She said that real-world evidence shows that CGM adoption is cost-neutral among Medicaid programs. She said that another study shows a 0.6% HbA1c reduction after 12 months use of CGM. She said that Abbott has more data to showcase the benefits of CGM.

Hodges asked the appointed experts to weigh in. Gingerich real aloud the biographical statements of the three ad-hoc experts:

Barbara Hettinger, MD, PhD, is an endocrinologist at the Portland Veterans Affairs Medical Center, specializing in diabetes. She is in active practice and prescribes continuous glucose monitors, which are under review today. Dr. Hettinger is also the Associate Program Director OHSU's Endocrinology, Diabetes and Clinical Nutrition Fellowship program, and she serves on local committees to develop criteria for use of continuous glucose monitors. She has no conflicts of interest to declare.

Laura Lacey, PharmD, is a clinical pharmacist and diabetes specialist. In 2019 she joined the St. Charles Medical Group in Bend. Dr. Lacey utilizes continuous glucose monitors in her regular practice and works under a collaborative practice agreement to provide specialized diabetes management, including insulin pump and continuous glucose monitor management. She has no conflicts of interest to declare.

Kimberly Cleveland, RN, is a diabetes educator at Samaritan Lebanon Community Hospital. Her specialties include diabetes management and diabetes foot care. Ms. Cleveland conducts group classes and individual sessions on diabetes self-management education and provides training on the use of personal continuous glucose monitors. She serves as the Advocacy Co-Chair for the Oregon chapter of Association of Diabetes Specialists. She has submitted legislative testimony in favor of CGM coverage in Oregon's current legislative session.

Lacey said that there needs to be more clarity in the pharmacy PA request process and if provider documentation attesting to use will be sufficient. Hodges said that the utilization documentation would require a download of the monitor's utilization, as is the case with other DME devices that require adherence compliance, such as CPAP. There was a discussion of whether providers would actually have the ability to look at such a download, and whether it was practical during a short visit.

The subcommittee continued to discuss the draft recommendation, including the EbGS's decision to narrow the eligible population to those who require multiple daily doses of insulin. EbGS initially considered noncoverage as their recommendation given the low strength of the evidence, and decided to recommend coverage for a narrower subset given the large expected utilization for this device and the high cost associated with CGM. After discussing several

alternatives, the subcommittee clarified that CGM would be covered for patients requiring either short-acting or intermediate-acting doses of insulin.

Collins disclosed his personal interest given that he is a CGM user and said that when he was doing finger sticks, he would not be checking as often as he should. Now that he wears a CGM, he gets an alarm when he gets a low level.

Walker said there was a CGM coverage mandate bill this past legislative session which had recommended more than two daily insulin doses per day in order to be eligible for CGM. Irwin said she is struggling between the available evidence and the pragmatic decisions taken today. Pinzon said that CGM is a powerful tool and getting feedback is useful. Schabel said that given that EbGS went from a no-coverage recommendation to a recommendation of coverage among those who are on multiple insulin doses is compelling for her. She moved to approve the draft coverage guidance as modified for referral for HERC consideration.

Recommended Actions:

1) Add the following CPT codes to Line 1 PREGNANCY and Line 27 TYPE 2 DIABETES MELLITUS effective 1/1/2024
    a. 95249 Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of 72 hours; patient-provided equipment, sensor placement, hook-up, calibration of monitor, patient training, and printout of recording
    b. 95250 Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of 72 hours; physician or other qualified health care professional (office) provided equipment, sensor placement, hook-up, calibration of monitor, patient training, removal of sensor, and printout of recording
    c. 95251 Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of 72 hours; analysis, interpretation and report
2) Add the following HCPCS codes to the ANCILLARY PROCEDURES file effective 1/1/24
    a. A4238 Supply allowance for adjunctive, non-implanted continuous glucose monitor (CGM), includes all supplies and accessories necessary for use of the device (i.e., sensors, transmitter); 1 month supply = 1 unit of service
    b. A4239 Supply allowance for non-adjunctive, non-implanted continuous glucose monitor (CGM), includes all supplies and accessories necessary for use of the device (i.e., sensors, transmitter); 1 month supply = 1 unit of service
    c. E2102 Adjunctive, non-implanted continuous glucose monitor or receiver; May be covered once every 3 years
    d. E2103 Non-adjunctive, non-implanted continuous glucose monitor or receiver; May be covered once every 3 years
3) Modify guideline note 108 as shown in Appendix A

MOTION: To approve the recommendations as modified. CARRIES 6-0.

Public Comment

No additional public comment was received.

Issues for next meeting

- Breast reduction for macromastia
- PSMA PET scans for prostate cancer
- Cardiac resynchronization therapy
- Nasal fracture repair
- Treatment of liver metastases

Next meeting

November 9, 2023, online and Clackamas Community College, Wilsonville, OR.

Adjournment

The meeting adjourned at 1:00 PM.

Appendix A
Revised Guideline Notes

GUIDELINE NOTE 21, SEVERE INFLAMMATORY SKIN DISEASE

Lines 426,482,504,533,542,555,656

Inflammatory skin conditions included in this guideline are:

A) Psoriasis
B) Atopic dermatitis
C) Lichen planus
D) Darier disease
E) Pityriasis rubra pilaris
F) Discoid lupus
G) Vitiligo
H) Prurigo nodularis
I) Ichthyosis

The conditions above are included on Line 426 if severe, defined as having functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's Dermatology Life Quality Index (CDLQI) ≥ 13 (or severe score on other validated tool) AND one or more of the following:

A) At least 10% of body surface area involved
B) Hand, foot, face, or mucous membrane involvement.

Otherwise, these conditions above are included on Lines 482, 504, 533, 542, 555 and 656.

For severe psoriasis, treatments included on this line are topical agents, phototherapy, targeted immune modulator medications and other systemic medications.

For severe atopic dermatitis/eczema, treatments included on this line are topical moderate- to high-potency corticosteroids, topical calcineurin inhibitors (for example, pimecrolimus, tacrolimus), narrowband UVB, topical phosphodiesterase (PDE)-4 inhibitors, and oral immunomodulatory therapy (e.g., cyclosporine, methotrexate, or oral corticosteroids). Targeted immune modulators (for example, dupilumab) are included on this line when:

A) Prescribed in consultation with a dermatologist or allergist or immunologist, AND
B) The patient has failed (defined as inadequate efficacy, intolerable side effects, or side effects that pose a health risk) either
    1) a 4 week trial of a combination of topical moderate to high potency topical steroids and a topical non-steroidal agent OR
        an oral immunomodulator, OR
    2) 12 weeks of phototherapy.

JAK inhibitor (upadacitinib) therapy is included on this line when other immunomodulatory therapy has failed to adequately control disease (defined as inadequate efficacy, intolerable side effects, or side effects that pose a health risk).

ICD-10-CM Q82.8 (Other specified congenital malformations of skin) is included on Line 426 only for Darier disease.

Appendix A
Revised Guideline Notes

~~**GUIDELINE NOTE 93, IMPLANTABLE GNRH ANALOG THERAPY**~~

~~*Line 187*~~

~~Use of drug delivery implant therapy for GnRH analogue therapy (such as histrelin) (CPT 11981-11983) is covered only when injectable depot medications (such as Lupron) are contraindicated or after such medications have been tried and complications preclude further use.~~

[changes in red made at the September 28, 2023 HERC meeting]

GUIDELINE NOTE 106, PREVENTIVE SERVICES

Lines 3,622

Included on Line 3 are the following preventive services:

A) US Preventive Services Task Force (USPSTF) "A" and "B" Recommendations in effect and issued prior to January 1, 2022.
   1) https://www.uspreventiveservicestaskforce.org/uspstf/recommendation-topics/uspstf-a-and-b-recommendations/
      a) Treatment of falls prevention with exercise interventions is included on Line 292.
   2) USPSTF "D" recommendations are not included on this line or any other line of the Prioritized List.

B) American Academy of Pediatrics (AAP) Bright Futures Guidelines:
   1) http://brightfutures.aap.org. Periodicity schedule available at https://downloads.aap.org/AAP/PDF/periodicity_schedule.pdf
      a) Bright Futures is the periodicity schedule for screening for EPSDT for the Oregon Health Plan.
   2) Screening for lead levels is defined as blood lead level testing and is indicated for Medicaid populations at 12 and 24 months. In addition, blood lead level screening of any child between ages 24 and 72 months with no record of a previous blood lead screening test is indicated.

C) Health Resources **and Services Administration (HRSA) Women's Preventive Services-Required Health Plan Coverage Guidelines (revised** January 2022). Available at https://www.hrsa.gov/womens-guidelines as of July 28, 2022.

D) Immunizations as recommended by the Advisory Committee on Immunization Practices (ACIP): http://www.cdc.gov/vaccines/schedules/hcp/index.html or approved for the Oregon Immunization Program:
~~https://public.health.oregon.gov/PreventionWellness/VaccinesImmunization/ImmunizationProviderResources/Documents/DMAPvactable.pdf~~
https://www.oregon.gov/oha/ph/preventionwellness/vaccinesimmunization/immunizationproviderresources/pages/payor.aspx
   1) COVID-19 vaccines are intended to be included on this line even if the specific administration code(s) do not yet appear on the line when the vaccine has both 1) FDA approval or FDA emergency use authorization (EUA) and 2) ACIP recommendation.

2) Other ACIP recommended vaccines not on the routine vaccine schedule are covered as specified in the MMWR as required by federal law: https://www.cdc.gov/vaccines/hcp/acip-recs/index.html

Colorectal cancer screening is included on Line 3 for average-risk adults aged 45 to 75, using one of the following screening programs:

A) Colonoscopy every 10 years
B) Flexible sigmoidoscopy every 5 years
C) Fecal immunochemical test (FIT) every year
D) Guaiac-based fecal occult blood test (gFOBT) every year

Screening CT colonography (CPT 74263) is only covered for patients who are unable to complete a screening colonoscopy due to colon structural problems (for example, colonic obstruction, stricture, or compression or tortuous or redundant colon) ~~on the same day at the CT colonography is done.~~

~~CT colonography (CPT 74263),~~ FIT-DNA (CPT 81528) and mSEPT9 (HCPCS G0327) are included on Line 502 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS.

Colorectal cancer screening for average-risk adults aged 76 to 85 is covered after informed decision making between patients and clinicians which includes consideration of the patient's overall health, prior screening history, and preferences.

Supervised evidence-based exercise programs for fall prevention for persons aged 65 or older OR younger patients who are at increased risk of falls are included on Line 3 using CPT 98961 or 98962 or HCPCS S9451. HCPCS S9451 is only included on Line 3 for the provision of supervised exercise therapy for fall prevention. Programs should be culturally tailored/culturally appropriate when feasible.

Note: CPT 96110 (Developmental screening (e.g., developmental milestone survey, speech and language delay screen), with scoring and documentation, per standardized instrument) can be billed in addition to other CPT codes, such as evaluation and management (E&M) codes or preventive visit codes.

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

Guideline Note 108, CONTINUOUS GLUCOSE MONITORING

Lines 1, 8, 27, 60

Real-time (personal) continuous glucose monitoring (CGM) is included on Line 8 for:

A. Adults with type 1 diabetes mellitus not on insulin pump management:
   1. Who have received or will receive diabetes education specific to the use of CGM AND
   2. Who have used the device for at least 50% of the time at their first follow-up visit AND
   3. Who have baseline HbA1c levels greater than or equal to 8.0%, frequent or

severe hypoglycemia, or impaired awareness of hypoglycemia (including presence of these conditions prior to initiation of CGM).

B. Adults with type 1 diabetes on insulin pump management (including the CGM-enabled insulin pump):
   1. Who have received or will receive diabetes education specific to the use of CGM AND
   2. Who have used the device for at least 50% of the time at their first follow-up visit.
C. Women with type 1 diabetes who are pregnant or who plan to become pregnant within six months without regard to HbA1c levels.
D. Children and adolescents under age 21 with type 1 diabetes:
   1. Who have received or will receive diabetes education specific to the use of CGM AND
   2. Who have used the device for at least 50% of the time at their first follow-up visit

Therapeutic continuous glucose monitors are included on Lines 1 and 27 for individuals with type 2 diabetes or gestational diabetes who use short- or intermediate-acting insulin injections when ALL of the following criteria are met:

A. Have received or will receive diabetes education specific to the use of CGM, AND
B. Have used the device for at least 50% of the time for a 90-day period by their first follow-up visit (within 3-6 months), AND
C. Have one of the following at the time of CGM therapy initiation:
   1. Baseline HbA1c levels greater than or equal to 8.0%, OR
   2. Frequent or severe hypoglycemia, OR
   3. Impaired awareness of hypoglycemia (including presence of these conditions prior to initiation of CGM), OR
   4. Diabetes-related complications (for instance, peripheral neuropathy, end-organ damage)

Every 6 months following the initial prescription for CGM, the prescriber must conduct an in-person or telehealth visit with the member to document adherence to their CGM regimen to ensure that CGM is used for diabetes treatment planning.

Two trials per year of CGM are allowed to meet adherence for continuation of coverage.

CPT 95250 and 95251 (Ambulatory continuous glucose monitoring) are included on ~~this line~~ these lines for services related to real-time continuous glucose monitoring but not retrospective (professional) continuous glucose monitoring.

~~Continuous glucose monitors are not covered for people with type 2 diabetes or gestational diabetes.~~

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.

Appendix A
Revised Guideline Notes

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

Line 662

The following Interventions are prioritized on Line 662 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
A0475, E0446	Topical oxygen therapy	Insufficient evidence of effectiveness	September2023
A9268, A9269	Ingestible vibrating devices for the treatment of constipation	Insufficient evidence of effectiveness	September 2023
A9292	Prescription digital visual therapy for amblyopia	Insufficient evidence of effectiveness	September 2023
C9788	Optoacoustic breast imaging	Insufficient evidence of effectiveness	September 2023
C9790	Histotripsy for malignant renal tissue	Insufficient evidence of effectiveness	September 2023
C9791	Magnetic resonance imaging with inhaled hyperpolarized xenon-129 contrast agent, chest, including preparation and administration of agent	Insufficient evidence of effectiveness	September 2023
E0490, E0491, K1028, K1029	Daytime intraoral neuromuscular electrical tongue stimulation for snoring and obstructive sleep apnea	Insufficient evidence of effectiveness	September 2023
S8930 0720T	Electrical stimulation of auricular acupuncture points by proprietary electrical stimulation devices, such as P-Stim and E-pulse [note: auricular electroacupuncture provided by a licensed provider in a clinical setting is covered under CPT 97813-97814] Percutaneous electrical nerve field stimulator (PENFS), percutaneous electrical nerve stimulation (PENS) and percutaneous neuromodulation therapy (PNT) for irritable bowel syndrome (for example, IB-Stim)	No evidence of effectiveness	March, 2018 September 2023 for IBS indications

Appendix A
Revised Guideline Notes

Procedure Code	Intervention Description	Rationale	Last Review
0275T G0276	Percutaneous laminotomy/laminectomy (interlaminar approach) for decompression of neural elements (with or without ligamentous resection, discectomy, facetectomy and/or foraminotomy), any method under indirect image guidance (eg, fluoroscopic, CT), single or multiple levels, unilateral or bilateral; lumbar Blinded procedure for lumbar stenosis, PILD, or placebo control, performed in an approved coverage with evidence development (CED) clinical trial	Insufficient evidence of effectiveness	~~October 2021~~ November 2023
~~31647-31649, 31651~~	~~Bronchial valve insertion/removal/replacement~~	~~Insufficient evidence of effectiveness~~	~~December, 2012~~
~~74261-74262~~	~~Computed tomographic (CT) colonography~~		~~December, 2009~~
~~74263,~~ 81528, 81327, G0327	~~Screening CT colonography,~~ FIT-DNA (Cologuard), mSEPT9, Chromoscopy	Insufficient evidence for use in population screening	~~August 2021~~ August 2923

GUIDELINE NOTE 221, DEEP BRAIN STIMULATION FOR TREATMENT OF REFRACTORY EPILEPSY

Line 174

Deep brain stimulation for treatment of refractory epilepsy is included on this line only when

A) The surgery is performed at a Level 4 epilepsy center, AND

B) The patient has failed ~~multiple (three~~ two or more~~)~~ anti-seizure medications, AND

C) The patient is ineligible for resective surgery OR has failed vagus nerve stimulation or resective surgery.

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

GUIDELINE NOTE 228, PANDAS, PANS AND AUTOIMMUNE ENCEPHALITIS

Line 313

ICD-10-CM G04.82 (Other encephalitis and encephalomyelitis) is only included on this line for autoimmune encephalitis and related non-PANDAS/PANS conditions and is not included in this

guideline. Autoimmune encephalitis must meet established diagnostic criteria (for example, the International Encephalitis Consortium 2013 diagnostic criteria).

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) is included on this line when coded with ICD-10-CM D89.89 (Other specified disorders involving the immune mechanism, not elsewhere classified). Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS) is included on this line when coded with ICD-10-CM D89.9 (Disorder involving the immune mechanism, unspecified).

Up to 3 monthly immunomodulatory courses of intravenous immunoglobulin (IVIG) therapy is included on this line to treat PANDAS and PANS when both of the following are met:

A) A clinically appropriate trial of two or more less-intensive treatments (for example, appropriate limited course of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, selective serotonin reuptake inhibitors (SSRIs), behavioral therapy, short-course antibiotic therapy) was either not effective, not tolerated, or did not result in sustained improvement in symptoms (as measured by a lack of clinically meaningful improvement on a validated instrument directed at the patient's primary symptom complex). These trials may be done concurrently, AND
B) A consultation with and recommendation from a pediatric subspecialist (for example, pediatric neurologist, pediatric psychiatrist, pediatric mental health nurse practitioner, neurodevelopmental pediatrician, pediatric rheumatologist, pediatric allergist/immunologist, as well as the recommendation of the patient's primary care provider (for example, family physician, pediatrician, pediatric or family nurse practitioner, family or pediatric physician assistant, naturopathic physician). The subspecialist consultation may be a teleconsultation. For adolescents, an adult subspecialist consult may replace a pediatric subspecialist consult.

A reevaluation at 3 months by both the primary care provider and pediatric expert is required for continued therapy of IVIG. This evaluation must include clinical testing with a validated instrument, which must be performed pretreatment and posttreatment to demonstrate clinically meaningful improvement.

Long term antibiotic therapy is not included on this line for treatment of PANDAS/PANS.

Therapeutic plasma exchange (CPT 36514) does not pair with PANDAS or PANS (ICD-10-CM D89.89 or D89.9).

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

Appendix B
NEW GUIDELINE NOTES

[changes in red made at the September 28, 2023 HERC meeting]

DIAGNOSTIC GUIDELINE DX, DIAGNOSTIC CT COLONOGRAPHY

Diagnostic CT colonography (CPT 74261-74262) is covered for evaluation of symptomatic individuals who

1) Are unable to undergo colonoscopy due to known structural problems (for example, colonic obstruction, stricture, or compression or tortuous or redundant colon); OR
2) Who were unable to complete a diagnostic colonoscopy due to colon structural problems ~~on the same day that the CT colonography is done.~~

[changes in red and blue made at the September 28, 2023 HERC meeting]

GUIDELINE NOTE XXX ENDOBRONCHIAL VALVES

Line 283

Endobronchial valves (CPT 31647-31649 and 31651) are only included on this line when ALL of the following criteria are met:

1) The patient has severe heterogeneous or homogeneous emphysema
    a) Severe emphysema is demonstrated by pulmonary function testing showing
        i) Forced expiratory volume in one second (FEV 1) ≤ 45% predicted and, if age 70 or older, FEV 1≥ 15% predicted value
        ii) Total lung capacity (TLC) ≥ 100% predicted post-bronchodilator
        iii) Residual volume (RV) ≥ 150% predicted post-bronchodilator
2) The patient has significant hyperinflation in regions of the lung that have little to no collateral ventilation
3) The patient is receiving optimized medical care
4) The patient is stable with ≤20 mg prednisone (or equivalent) dose a day
5) The patient has participated in pulmonary rehabilitation and has a post-rehabilitation 6-min walk of ≥ 140 m
6) ~~The patient is a non-smoker or abstinent from all nicotine products for 6 months prior to surgery, as shown by negative cotinine levels at least 6 months apart, with the second test within 1 month of the procedure date~~
7) The patient is a non-smoker as determined by the performing provider

DIAGNOSTIC GUIDELINE DX, NEXT GENERATION SEQUENCING OF MALIGNANCIES

Next Generation Sequencing (NGS, for example CPT 81479, 81455, 0037U) is covered when all of the following requirements are met:

1) The patient has
    a. Either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; AND
    b. Has not been previously tested using the same NGS test for the same primary diagnosis of cancer, unless the criteria in 4) below are met; AND

   c. Decided to seek further cancer treatment (for example, therapeutic chemotherapy) and has adequate performance status (ECOG 0-2) to undergo such treatment; AND

2) The diagnostic laboratory test using NGS must have:
   a. Clinical Laboratory Improvement Amendments (CLIA)-certification; AND
   b. The test is being used as a companion diagnostic test in accordance with Food & Drug Administration (FDA)-approved therapeutic labeling; AND
   c. Results provided to the treating physician for management of the patient using a report template to specify treatment options; AND
3) A single CPT or HCPCS code is covered for each multigene panel performed on tumor tissue. Additional codes for individual genes and for molecular pathology procedures CPT 81400-81408 are excluded from coverage when the multigene panel is covered under the appropriate CPT or HCPCS code.
4) Repeat NGS testing may be required in the setting of patients who have clinically progressed per standardized professional guidelines after therapy. Coverage in this situation is limited to 3 times per primary malignancy unless there is indication for additional testing after individualized review of medical necessity.

Section 2.0

Staff Report

Section 3.0

Plain Language Summaries

Value-based Benefits Subcommittee (VbBS)
Plain Language Summary of Topics
November 9, 2023

This plain language summary provides a short and non-technical explanation of the topics that will be discussed at the meeting, along with the staff recommendations. Decisions are not final unless approved by the Health Evidence Review Commission (which usually meets later on the same day). The Commission may approve, modify, or not approve staff recommendations.

OHAP Straightforward Guideline Note Changes

Plain Language Summary:

Coverage question: Should OHP cover a medical procedure to clip a small piece of tissue under the lip (frenulectomy/frenulotomy) for patients ages 12-21?

Should OHP cover this treatment? Yes, staff propose covering if the patient has receding gums, a condition when gum tissue starts to pull back and wear away from teeth.

BHAP Straightforward Code Change

Plain Language Summary:

Coverage question: Should OHP cover therapy given in a group setting for autism treatment?

Should OHP cover this treatment? Yes, staff recommend that this should be covered.

Problem Related to Unspecified Psychosocial Circumstances

Plain Language Summary:

Coverage question: Should OHP cover a non-specific mental health and social condition?

Should OHP cover this treatment? Yes, staff suggest covering this as multiple groups in Oregon recommend covering this condition.

Value-based Benefits Subcommittee (VbBS)
Plain Language Summary of Topics
November 9, 2023

Transcranial Magnetic Stimulation (TMS) 2023 Review

Plain Language Summary:

Coverage question: TMS uses magnets to create a strong, targeted electric current in certain parts of the brain. which may help improve mental health conditions including depression. Should OHP:
1) Increase the number of treatments allowed?
2) Cover TMS for obsessive compulsive disorder (OCD)?
3) Cover TMS for people under 21 with severe depression?
4) Change the requirements for getting TMS?

Should OHP cover these treatments? Staff recommends:
1) Yes, the number of sessions should be increased by 6.
2) No, there is not any data showing that TMS works for OCD.
3) No, the data is still emerging for this age group.
4) Yes, change the requirements a trial of one medication and a second treatment trial, which could be a medication or therapy.

Hereditary Cancer Genetic Testing Guideline Update

Plain Language Summary:

Coverage question: Should OHP make major changes to the guideline on medical testing that helps determine a higher risk of developing certain types of cancer due to their family's genetic history.

Should OHP cover these tests? Yes, staff suggests adding tests recommended by a national expert group for 37 conditions, letting them simplify the guideline. In addition, strike the section about rush testing and strike the wording that requires "suitably trained" health professionals.

Value-based Benefits Subcommittee (VbBS)
Plain Language Summary of Topics
November 9, 2023

Genetic Testing for Developmental Disabilities, Intellectual Disability, and Autism Spectrum Disorder

Plain Language Summary:

Coverage question: Should OHP update the guideline on medical testing that helps decide a higher risk of developing certain types of disabilities or disorders?

Should OHP cover these tests? Staff recommends no changes to the guideline. There are still problems with the large genetic tests for X linked disorders.

OncoExTra

Plain Language Summary:

Coverage question: Should OHP cover a medical testing that helps figure out the risk for advanced cancer (OncoExTra)?

Should OHP cover this treatment? Yes, staff recommend covering as similar tests using more generic codes are already covered.

Computer Assisted Bronchoscopy 2023 Review

Plain Language Summary:

Coverage question: Should OHP cover a procedure that uses computer pictures to help guide where a doctor looks in the lungs to get sample tissue?

Should OHP cover this treatment? Yes, newly published medical studies show this procedure is both safe and accurate.

Value-based Benefits Subcommittee (VbBS)
Plain Language Summary of Topics
November 9, 2023

Anterior Thoracic Vertebral Body Tethering

Plain Language Summary:

Coverage question: Should OHP cover a medical process to attach a device to the bones of the spine to treat abnormal curves of the spine?

Should OHP cover this treatment? No, the risks for this process are too high and it is considered not yet proven (experimental) by private insurance.

Posterior Nasal Nerve Ablation

Plain Language Summary:

Coverage question: Should OHP cover a medical process to destroy a nerve that can cause a constant runny nose?

Should OHP cover this treatment? No. The process is not well-studied, and it is considered not yet proven (experimental) by private insurance.

Phrenic Nerve Stimulator

Plain Language Summary:

Coverage question: Should OHP cover a device that uses electrical pulse to make the nerve a in the neck work better to help a person who is using a breathing machine?

Should OHP cover this treatment? Yes. This is a standard option for treatment of certain patients who are very ill.

Value-based Benefits Subcommittee (VbBS)
Plain Language Summary of Topics
November 9, 2023

Urethral Stricture Dilation with Drug-Coated Balloon Catheter

Plain Language Summary:

Coverage question: Should a procedure that uses a tube coated with medicine to open the urethra be covered?

Should OHP cover this treatment? No, this procedure is not well studied.

Transcervical Ablation of Uterine Fibroids

Plain Language Summary:

Coverage question: Should OHP cover a medical procedure to destroy noncancer growths in the uterus?

Should OHP cover this treatment? No, evidence does not support this specific medical procedure.

Suprachoroidal Injections

Plain Language Summary:

Coverage question: Should OHP cover a certain way to deliver medication to the back of the eye?

Should OHP cover this treatment? Yes, for treatment of a condition where there's swelling in the center part of the eye (the macula) caused by inflammation (uveitic macular edema).

Value-based Benefits Subcommittee (VbBS)
Plain Language Summary of Topics
November 9, 2023

Coronary Lithotripsy

Plain Language Summary:

Coverage question: Should OHP cover a medical procedure to help open blocked blood vessels to the heart?

Should OHP cover this treatment? No. It has not been compared to more common treatments and no studies found evidence of it working well.

Enhanced Liver Fibrosis (ELF) Test

Plain Language Summary:

Coverage question: Should OHP cover a certain test to check on the health of the liver?

Should OHP cover this treatment? Maybe, this is one good way to test for advanced liver disease but costs more than other tests.

HIPEC

Plain Language Summary:

Coverage question: Should OHP cover a treatment for certain types of advanced cancer? Doctors heat up a special chemotherapy medicine and put it directly into the abdomen (peritoneum) to treat cancer that might be there. The heat and the medicine together can help fight the cancer.

Should OHP cover this treatment? Yes, the advantages of treatment are greater than the potential harms for certain advanced cancers.

Value-based Benefits Subcommittee (VbBS)
Plain Language Summary of Topics
November 9, 2023

Breast Reduction for Macromastia

Plain Language Summary:

Coverage question: Should OHP cover surgery to reduce the size of breasts when they cause back and/or neck pain?

Should OHP cover this treatment? Yes, when there are no other reasons for the neck and back pain, and in situations where the surgery seems likely to help with the neck and back pain this surgery should be covered.

Gender Affirming Treatment Standard of Care

Plain Language Summary:

Coverage question: Should OHP pick a "standard of care" for gender affirming treatments?

Should OHP cover this treatment? Yes, OHP should use the World Professional Association for Transgender Health (WPATH) Standards of Care 8.0.

Tobacco Cessation Requirements in Prioritized List Guidelines

Plain Language Summary:

Coverage question: Should OHP members have to stop smoking or using nicotine before they can have certain types of surgery?

Should OHP cover this treatment? Yes, with some changes for spinal fusion and lung surgery for COPD. No, for surgery for erectile dysfunction.

Value-based Benefits Subcommittee (VbBS)
Plain Language Summary of Topics
November 9, 2023

PET Scan for Prostate Cancer

Plain Language Summary:

Coverage question: Should OHP cover a specific type of imaging test to see whether prostate cancer has spread to other parts of the body?

Should OHP cover this treatment? Yes, for people diagnosed with more severe forms of prostate cancer.

Cardiac Resynchronization Therapy

Plain Language Summary:

Coverage question: Should OHP clarify the requirements for treatments that helps the heart beat with the right rhythm (pacemaker and heart defibrillator).

Should OHP make this change? Yes.

Nasal Fracture Coverage Clarification

Plain Language Summary:

Coverage question: Should OHP cover treatments for a broken nose?

Should OHP cover this treatment? Yes, fixing a broken nose may need adjusting by hand, with or without using splints. This should be done within 14 days after the break happened. Rhinoplasty (a nose surgery) is needed when the nose is blocked and causing breathing problems.

Value-based Benefits Subcommittee (VbBS)
Plain Language Summary of Topics
November 9, 2023

Treatment of Liver Metastases

Plain Language Summary:

Coverage question: Liver metastases are tumors that started out in some other part of the body and have spread to the liver. Should OHP cover treatments for this condition?

Should OHP cover these treatments? Yes, certain types of treatments should be covered in limited cases.

Foot and Toenail Care for Patients in Facilities

Plain Language Summary:

Coverage question: Should OHP cover nail and foot care for people who live in nursing homes?

Should OHP cover this treatment? Certain conditions should be covered because active fungal infections in a nursing home can be passed from patient to patient and is a public health issue.

Central Auditory Function Testing

Plain Language Summary:

Coverage question: Should OHP cover testing for a condition that makes it difficult for a person to understand speech and follow instructions, especially when there is a lot of noise around.

Should OHP cover this treatment? No. The problem is a bit unclear, and even the experts can't decide on a consistent way to identify it. There are no widely accepted tests, and there are no medications for this condition. Other health plans are not covering this condition.

Value-based Benefits Subcommittee (VbBS)
Plain Language Summary of Topics
November 9, 2023

Photoscreening 2023

Plain Language Summary:

Coverage question: Should OHP cover a test (photoscreening) that checks a child's vision using a special camera instead of an eye chart? It helps find out how well a child can see.

Should OHP cover this test?
Option 1: No. This test is not as cost-effective as using an eye chart for screening.
Option 2: Yes, cover this test because experts recommend it.

Severe Exfoliating Skin Conditions

Plain Language Summary:

Coverage question: Should OHP cover severe shedding of the skin that can affect overall health?

Should OHP cover this treatment? Yes, based on expert input.

Refugee Screening

Plain Language Summary:

Coverage question: Should OHP cover medical screenings for people arriving from other countries who are seeking safety and protection from war or other dangers?

Should OHP cover this treatment? Yes, this screening is a federal requirement.

Section 4.0

Consent Agenda-

Straightforward Items

Consent Agenda Issues—November 2023

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
82306	Vitamin D; 25 hydroxy, includes fraction(s), if performed	59 END STAGE RENAL DISEASE	Vitamin D testing was reviewed in 2011 as part of the Oregon Health Leadership Council effort to reduce waste in the medical system. Vitamin D testing was restricted to certain conditions. One condition listed as appropriate by the OHLC was chronic kidney disease stage III or greater. 82306 current does not appear on the end state kidney disease line. Multiple denials were found on the most recent HSD denials summary for this pairing. 82306 does appear on line 399 CHRONIC KIDNEY DISEASE	Add 82306 to line 59
26426 26428	Repair of extensor tendon, central slip, secondary (eg, boutonniere deformity); using local tissue(s), including lateral band(s), each finger Repair of extensor tendon, central slip, secondary (eg, boutonniere deformity); with free graft (includes obtaining graft), each finger	377 DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF-DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION	ICD-10-CM M20.02X (Boutonniere deformity) is on line 377. Repair of this deformity is not pairing and causing need for medical review	Add 24626 and 26427 to line 377
46922	Simple removal of growth of anus	ANAL, RECTAL AND COLONIC POLYPS	46922 should pair with ICD-10-CM K62.0 (Anal polyp). Several other anal polyp removal codes are on line 166	Add 46922 to line 166
M53.3	Sacrococcygeal disorders, not elsewhere classified	395 SEVERE SACROILIITIS	Hearings received a request to pain M53.3 with CPT 27279 (SI joint fusion). M53.3 contains sub-diagnoses for SI joint pain. Adding M53.3 to line 395 will allow surgery only if guideline criteria are met	Add M53.3 to line 395

Straightforward CGM Code Cleanup

Issue: The HERC modified the continuous glucose monitors guideline to clarify that only therapeutic devices are covered at their 9/28/23 meeting. The non-therapeutic (also known as adjunctive) codes were not removed from the initial staff recommendation. The non-therapeutic devices should not be covered.

HERC staff recommendations:

1) Remove the following HCPCS codes from ANCILLARY PROCEDURES file and add to line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
    a. A4238 Supply allowance for adjunctive, non-implanted continuous glucose monitor (CGM), includes all supplies and accessories necessary for use of the device (i.e., sensors, transmitter); 1 month supply = 1 unit of service
    b. E2102 Adjunctive, non-implanted continuous glucose monitor or receiver; May be covered once every 3 years
2) Add an entry to GN173 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 662

The following Interventions are prioritized on Line 662 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
A4238 E2102	Non-therapeutic continuous glucose monitors	Insufficient evidence of effectiveness	November 2023

Straightforward NCCN Guideline Update

Issue: The guideline on prophylactic treatment for prevention of breast cancer in high-risk women requires an update to the latest NCCN version of the breast, ovarian and pancreatic genetic testing guideline.

HERC staff recommendation:

1) Update Guideline Note 3 as shown below

GUIDELINE NOTE 3, PROPHYLACTIC TREATMENT FOR PREVENTION OF BREAST CANCER IN HIGH-RISK WOMEN

Line 191

Bilateral prophylactic breast removal and/or salpingo-oophorectomy are included on Line 191 for women without a personal history of invasive breast cancer who meet the criteria in the NCCN Clinical Practice Guidelines in Oncology (Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic V2.2024 (9/27/23) ~~V1.2023 (9/7/22)~~ www.nccn.org). Prior to surgery, women without a personal history of breast cancer must have a genetics consultation as defined in section B of the DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE.

Contralateral prophylactic mastectomy is included on Line 191 for women with a personal history of breast cancer.

Hysterectomy is only included on Line 191 for women with a BRCA1 pathogenic/likely pathogenic variant who undergo the procedure at the time of risk reducing salpingo-oophorectomy.

November 2023 Straightforward Preventive Services Guideline Edits

Isssue: The preventive services guideline needs dates updated for the references to the USPSTF recommendations and for the HRSA recommendations.

HERC staff recommendation:

1) Modify GN106 as shown below
    a. USPSTF recommendations are mandated for coverage the calendar year after they are published
    b. HRSA last updated their recommendations in December 2022
        i. Accessed by HERC staff 10/30/23

GUIDELINE NOTE 106, PREVENTIVE SERVICES

Lines 3,622

Included on Line 3 are the following preventive services:

A) US Preventive Services Task Force (USPSTF) "A" and "B" Recommendations in effect and issued prior to January 1, 2023 ~~2022~~.
    1) https://www.uspreventiveservicestaskforce.org/uspstf/recommendation-topics/uspstf-a-and-b-recommendations/
        a) Treatment of falls prevention with exercise interventions is included on Line 292.
    2) USPSTF "D" recommendations are not included on this line or any other line of the Prioritized List.

B) American Academy of Pediatrics (AAP) Bright Futures Guidelines:
    1) http://brightfutures.aap.org. Periodicity schedule available at https://downloads.aap.org/AAP/PDF/periodicity_schedule.pdf
        a) Bright Futures is the periodicity schedule for screening for EPSDT for the Oregon Health Plan.
    2) Screening for lead levels is defined as blood lead level testing and is indicated for Medicaid populations at 12 and 24 months. In addition, blood lead level screening of any child between ages 24 and 72 months with no record of a previous blood lead screening test is indicated.

C) Health Resources and Services Administration (HRSA) Women's Preventive Services-Required Health Plan Coverage Guidelines (revised December 2022 ~~January 2022~~). Available at https://www.hrsa.gov/womens-guidelines as of ~~July 28, 2022~~ October 30, 2023.

D) Immunizations as recommended by the Advisory Committee on Immunization Practices (ACIP): http://www.cdc.gov/vaccines/schedules/hcp/index.html or approved for the Oregon Immunization Program: https://public.health.oregon.gov/PreventionWellness/VaccinesImmunization/ImmunizationProviderResources/Documents/DMAPvactable.pdf
    1) COVID-19 vaccines are intended to be included on this line even if the specific administration code(s) do not yet appear on the line when the vaccine has both 1) FDA approval or FDA emergency use authorization (EUA) and 2) ACIP recommendation.
    2) Other ACIP recommended vaccines not on the routine vaccine schedule are included on Line 3 when administered according to recommendations specified in the Morbidity and

November 2023 Straightforward Preventive Services Guideline Edits

Mortality Weekly Review (MMWR) as required by federal law: https://www.cdc.gov/vaccines/hcp/acip-recs/index.html (retrieved 8/8/2023).

Colorectal cancer screening is included on Line 3 for average-risk adults aged 45 to 75, using one of the following screening programs:

A) Colonoscopy every 10 years
B) Flexible sigmoidoscopy every 5 years
C) Fecal immunochemical test (FIT) every year
D) Guaiac-based fecal occult blood test (gFOBT) every year

CT colonography (CPT 74263), FIT-DNA (CPT 81528) and mSEPT9 (HCPCS G0327) are included on Line 502 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS.

Colorectal cancer screening for average-risk adults aged 76 to 85 is covered after informed decision making between patients and clinicians which includes consideration of the patient's overall health, prior screening history, and preferences.

Supervised evidence-based exercise programs for fall prevention for persons aged 65 or older OR younger patients who are at increased risk of falls are included on Line 3 using CPT 98961 or 98962 or HCPCS S9451. HCPCS S9451 is only included on Line 3 for the provision of supervised exercise therapy for fall prevention. Programs should be culturally tailored/culturally appropriate when feasible.

Note: CPT 96110 (Developmental screening (e.g., developmental milestone survey, speech and language delay screen), with scoring and documentation, per standardized instrument) can be billed in addition to other CPT codes, such as evaluation and management (E&M) codes or preventive visit codes.

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

Section 5.0

OHAP report

CDT code	Nomenclature	Descriptor	Comments	Recommended Placement
D0396	3D printing of a 3D dental surface scan	3D printing of a 3D dental surface scan to obtain a physical model.	Similar to D0470 (Diagnostic casts) which is Excluded. OHAP recommended coverage of D0470 as this is required as part of the orthodontic benefit Codes for the 3D scan itself is on line 256 (D0801-D0802 3d dental surface scan). OHAP felt these codes were best placed on the Diagnostic Procedures FIle	Diagnostic Procedures File **Add D0470 (Diagnostic casts) to Diagnostic Procedures File **Delete D0801-D0802 (3d dental surface scan) from line 256 DEFORMITIES OF HEAD AND HANDICAPPING MALOCCLUSION and place on the Diagnostic Procedures File
D1301	immunization counseling	A review of a patient's vaccine and medical history, and discussion of the vaccine benefits, risks, and consequences of not obtaining the vaccine. Counseling also includes a discussion of questions and concerns the patient, family, or caregiver may have and suggestions on where the patient can obtain the vaccine.	Dental office administration of vaccine CDT codes are included on line 3.	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
D2976	band stabilization – per tooth	A band, typically cemented around a molar tooth after a multi-surface restoration is placed, to add support and resistance to fracture until a patient is ready for the full cuspal coverage restoration.	Similar codes are on line 343	343 DENTAL CONDITIONS (E.G., CARIES, FRACTURED TOOTH) Treatment BASIC RESTORATIVE
D2989	excavation of a tooth resulting in the determination of non-restorability		Done as part of other treatment, should be bundled with other restorative codes.	343 DENTAL CONDITIONS (E.G., CARIES, FRACTURED TOOTH) Treatment BASIC RESTORATIVE

CDT code	Nomenclature	Descriptor	Comments	Recommended Placement
D2991	application of hydroxyapatite regeneration medicament – per tooth	Preparation of tooth surfaces and topical application of a scaffold to guide hydroxyapatite regeneration.	Dental group felt that this needs further research. HERC staff literature review found several evidence based reviews on hydroxyapatite which found that it can be beneficial in dental care products (toothpaste, mouthwash, etc.) but that its use in dentistry needs clinical trials.	646 DENTAL CONDITIONS WHERE TREATMENT RESULTS IN MARGINAL IMPROVEMENT Treatment ELECTIVE DENTAL SERVICES
D6089	accessing and retorquing loose implant screw - per screw		Part of implant care. DCO group had concerns that this is out of the allowed scope of care of general dentists	619 DENTAL CONDITIONS (E.G., MISSING TEETH) Treatment IMPLANTS
D7284	excisional biopsy of minor salivary glands		Used for diagnosis of a variety of conditions. May also have therapeutic purposes.	Diagnostic Procedures File
D7939	indexing for osteotomy using dynamic robotic assisted or dynamic navigation	A guide is stabilized to the teeth and/or the bone to allow for virtual guidance of osteotomy.	Osteotomy not covered; used for implant services.	619 DENTAL CONDITIONS (E.G., MISSING TEETH) Treatment IMPLANTS
D9938	fabrication of a custom removable clear plastic temporary aesthetic appliance		Cosmetic	645 DENTAL CONDITIONS WHERE TREATMENT IS CHOSEN PRIMARILY FOR AESTHETIC CONSIDERATIONS Treatment COSMETIC DENTAL SERVICES
D9939	placement of a custom removable clear plastic temporary aesthetic appliance		Cosmetic	645 DENTAL CONDITIONS WHERE TREATMENT IS CHOSEN PRIMARILY FOR AESTHETIC CONSIDERATIONS Treatment COSMETIC DENTAL SERVICES

CDT code	Nomenclature	Descriptor	Comments	Recommended Placement
D9954	fabrication and delivery of oral appliance therapy (OAT) morning repositioning device	Device for use immediately after removing a mandibular advancement device to aid in relieving muscle/jaw pain and occlusal changes.	OSA guideline: "Mandibular advancement devices (oral appliances) are covered for those for whom CPAP fails or is contraindicated" These devices are on line 202.	202 SLEEP APNEA, NARCOLEPSY AND REM BEHAVIORAL DISORDER Also add to line 202: **HCPCS K1027 (Oral device/appliance used to reduce upper airway collapsibility, without fixed mechanical hinge, custom fabricated, includes fitting and adjustment) **HCPCS E0486 (Oral device/appliance used to reduce upper airway collapsibility, adjustable or non-adjustable, custom fabricated, includes fitting and adjustment)
D9955	oral appliance therapy (OAT) titration visit	Post-delivery visit for titration of a mandibular advancement device and to subsequently evaluate the patient's response to treatment, integrity of the device, and management of side effects.	See D9954	202 SLEEP APNEA, NARCOLEPSY AND REM BEHAVIORAL DISORDER
D9956	administration of home sleep apnea test	Sleep apnea test, for patients who are at risk for sleep related breathing disorders and appropriate candidates, as allowed by applicable laws. Also, to help the dentist in defining the optimal position of the mandible.	Per the Board of Dentistry, this is outside the scope of practice for dentists in Oregon	Excluded File
D9957	screening for sleep related breathing disorders	Screening activities, performed alone or in conjunction with another evaluation, to identify signs and symptoms of sleep-related breathing disorders.	Per the Board of Dentistry, this is outside the scope of practice for dentists in Oregon	Excluded File

Denture, Crowns and Dental Implants

Coverage Question: Should any changes be made in current denture, crown or dental implant coverage?

Question source: OHP ombuds office, HERC staff listening session

Background: The OHP ombuds office has been collecting member complaints regarding dentures. These include difficulty in finding an OHP provider for dentures, barriers to replacing lost or stolen dentures, and barriers to obtaining partial dentures when molars but not front teeth are pulled. The ombuds office is requesting consideration of 1) allowing partial denture coverage for back teeth and 2) allowing more frequent replacement of dentures when dentures are lost or stolen.

Current coverage of dentures is limited to one set of full dentures every 10 years or partial dentures every 5 years) by rule, and by determination of the Oregon Legislature.

Dentures are governed by OAR 410-123-1260 (see Appendix A for the portion of the rule regarding dentures).

OHP members also brought up lack of coverage for dental implants at the HERC staff listening session.

Previous HSC/HERC reviews:

OHAP has periodically reviewed denture services as codes arise as new CDT codes. Implants have been discussed at various OHAP meetings in the past few years, mainly in the setting of a new CDT code related to implant services.

Current Prioritized List/Coverage status:

Complete dentures (CDT D5110, D5120) and resin-based partial dentures (CDT D5211, D5212) are on line 454 DENTAL CONDITIONS (E.G., MISSING TEETH, PROSTHESIS FAILURE) Treatment REMOVABLE PROSTHODONTICS (E.G., FULL AND PARTIAL DENTURES, RELINES)

Partial dentures with cast metal framework (CDT D5214, D5223, D5224) are on line 592 DENTAL CONDITIONS (E.G., CARIES, FRACTURED TOOTH) treatment ADVANCED RESTORATIVE-ELECTIVE (INLAYS, ONLAYS, GOLD FOIL AND HIGH NOBLE METAL RESTORATIONS)

Flexible base dentures (CDT D5225-D5228) are on line 646 DENTAL CONDITIONS WHERE TREATMENT RESULTS IN MARGINAL IMPROVEMENT Treatment ELECTIVE DENTAL SERVICES

Various dental implant CDT codes are on line 619 DENTAL CONDITIONS (E.G., MISSING TEETH) Treatment IMPLANTS (I.E., IMPLANT PLACEMENT AND ASSOCIATED CROWN OR PROSTHESIS)

Other payer policies:

Denture, Crowns and Dental Implants

Dentures (full or partial) are only covered for adults by only a few state Medicaid programs (Alaska, Idaho, Michigan, Louisiana, Montana, Nevada, New York, North Carolina, and South Dakota). Some of these state Medicaid programs have a dollar amount treatment cap of between $1,000 and $1,125.

Medicare does not pay for dentures, although some coverage may be obtained through a Medicare Advantage program.

Most commercial payers will require significant cost-sharing for dental implant coverage. Most Medicaid programs do not cover dental implants, considering them cosmetic. Some coverage may be obtained for children under the age of 21 through the EPSDT benefit.

OHAP input:

OHAP members are aware of frustration around coverage of dentures. Adult dentures are not a mandatory benefit under Medicaid by federal rule, and are only covered to the extent allowed by the Oregon Legislature. There are budgetary constraints to expanding benefits in these areas. Denture benefits are very expensive.

Suggestions for the most beneficial expansions of denture benefit would be to allow partial dentures for fewer numbers of missing teeth, when the front teeth are involved, or for missing premolars. There was discussion about allowing denture replacement sooner than currently allowed (10 years for full dentures) when the dentures are lost or stolen. However, it is already in rule that members may have more frequent denture replacement when stolen, lost in natural disaster, or in other circumstances outside of the member's control. However, the cost of earlier replacement may not be part of the rates for dental organizations. One area to focus future funding is on any additional funding on treatments to retain natural teeth, such as crowns after root canals. Currently, this benefit is very limited by age and type of teeth. Coverage of crowns other than stainless steel crowns, was cut years ago by rule/Legislative intent due to budget issues.

HERC staff recommendation:

1) This report is for situational awareness only. No changes are recommended currently to the denture, crown or dental implant benefit
2) Staff is working with other parts of OHA on whether it would be appropriate for HERC to address the budgetary dental limitations including crowns and dentures.

Denture, Crowns and Dental Implants

Appendix A
Except of OAR 410-123-1260 regarding dentures

(9) PROSTHODONTICS, REMOVABLE (D5000-D5899):

(a) Clients age 16 years and older are eligible for removable resin base partial dentures and full dentures;

(b) See OAR 410-123-1000 for detail regarding billing fabricated prosthetics;

(c) The fee for the partial and full dentures includes payment for adjustments during the six-month period following delivery to clients;

(d) Resin partial dentures:

(A) The Division may not approve resin partial dentures if stainless steel crowns are used as abutments;

(B) For clients through age 20, the client shall have one or more anterior teeth missing or four or more missing posterior teeth per arch with resulting space equivalent to that loss demonstrating inability to masticate. Third molars are not a consideration when counting missing teeth;

(C) For clients age 21 and older, the client shall have one or more missing anterior teeth or six or more missing posterior teeth per arch with Documentation by the provider of resulting space causing serious impairment to mastication. Third molars are not a consideration when counting missing teeth;

(D) The Dental Practitioner shall note the teeth to be replaced and teeth to be clasped when requesting Prior Authorization (PA).

(e) Replacement of removable partial or full dentures, when it cannot be made clinically serviceable by a less costly procedure (e.g., reline, rebase, repair, tooth replacement), is limited to the following:

(A) For clients at least 16 years of age, the Division shall replace:

(i) Full dentures once every ten years, only if Dentally Appropriate;

(ii) Partial dentures once every five years, only if Dentally Appropriate.

(B) The five- and ten-year limitations apply to the client regardless of the client's OHP or MCE enrollment status at the time the client's last denture or partial was received. For example: A client receives a partial on February 1, 2020 and becomes a FFS OHP client in 2023. The client is not eligible for a replacement partial until February 1, 2025. The client gets a replacement partial on February 3, 2025 while FFS and a year later enrolls in an MCE. The client would not be eligible for another partial until February 3, 2030, regardless of MCE or FFS enrollment;

(C) Replacement of partial dentures with full dentures is payable five years after the partial denture placement. Exceptions to this limitation may be made in cases of Acute trauma, natural disaster, or catastrophic illness that directly or indirectly affects the dental condition and results in additional tooth

loss. This pertains to, but is not limited to, cancer and periodontal disease resulting from pharmacological, surgical, and medical treatment for aforementioned conditions. Severe periodontal disease due to neglect of daily dental hygiene may not warrant replacement.

(f) The Division limits reimbursement of adjustments and repairs of dentures that are needed beyond six months after delivery of the denture as follows for clients 21 years of age and older:

(A) A maximum of four times per year for:

(i) Adjustments to dentures, per arch. Full and partial (D5410 - D5422);

(ii) Replace missing or broken teeth – complete denture, each tooth (D5520);

(iii) Replace broken tooth on a partial denture - each tooth (D5640);

(iv) Add tooth to existing partial denture (D5650).

(B) A maximum of two times per year for:

(i) Repair broken complete denture base (D5511, D5512);

(ii) Repair resin partial denture base (D5611, D5612);

(iii) Repair cast partial framework (D5621, D5622);

(iv) Repair or replace broken retentive/clasping materials – per tooth (D5630);

(v) Add clasp to existing partial denture – per tooth (D5660).

(g) Replace all teeth and acrylic on cast metal framework (D5670, D5671):

(A) Is covered for clients age 16 and older a maximum of once every ten (10) years, per arch;

(B) Ten years or more shall have passed since the original partial denture was delivered;

(C) Is considered replacement of the partial so a new partial denture may not be reimbursed for another ten years; and

(D) Requires Prior Authorization as it is considered a replacement partial denture.

(h) Denture rebase procedures:

(A) The Division shall cover rebases only if a reline may not adequately solve the problem;

(B) For clients through age 20, the Division limits payment for rebase to once every three years;

(C) For clients age 21 and older:

Denture, Crowns and Dental Implants

(i) There shall be Documentation of a current reline that has been done and failed; and

(ii) The Division limits payment for rebase to once every five years.

(D) The Division may make exceptions to this limitation in cases of Acute trauma or catastrophic illness that directly or indirectly affects the dental condition and results in additional tooth loss. This pertains to, but is not limited to, cancer and periodontal disease resulting from pharmacological, surgical, and medical treatment for aforementioned conditions. Severe periodontal disease due to neglect of daily dental hygiene may not warrant rebasing;

(i) Denture reline procedures:

(A) For clients through age 20, the Division limits payment for reline of complete or partial dentures to once every three years;

(B) For clients age 21 and older, the Division limits payment for reline of complete or partial dentures to once every five years;

(C) The Division may make exceptions to this limitation under the same conditions warranting replacement;

(D) Laboratory relines:

(i) Are not payable prior to six months after placement of an immediate denture;

(ii) For clients through age 20, are limited to once every three years;

(iii) For clients age 21 and older, are limited to once every five years.

(j) Interim partial dentures (also referred to as “flippers”):

(A) Are allowed if the client has one or more anterior teeth missing; and

(B) The Division shall reimburse for replacement of interim partial dentures once every five years but only when Dentally Appropriate.

(k) Tissue conditioning:

(A) Is allowed once per denture unit in conjunction with immediate dentures; and

(B) Is allowed once prior to new prosthetic placement.

(10) MAXILLOFACIAL PROSTHETIC SERVICES (D5900-D5999):

(a) Fluoride gel carrier is limited to those patients whose severity of dental disease causes the increased cleaning and fluoride treatments allowed in rule to be insufficient. The Dental Practitioner shall document failure of those options prior to use of the fluoride gel carrier;

Denture, Crowns and Dental Implants

(b) All other maxillofacial prosthetics (D5900-D5999) are medical services. Refer to OAR 410-123-1220:

(A) Bill for medical maxillofacial prosthetics using the professional (CMS1500, DMAP 505 or 837P) claim format;

(B) For clients receiving services through a CCO, PHP, or MCE bill medical maxillofacial prosthetics to the CCO, PHP, or MCE;

(C) For clients receiving medical services through FFS, bill the Division.

(11) ORAL & MAXILLOFACIAL SURGERY (D7000-D7999): Billing Procedures:

(a) Bill on a dental claim form using CDT codes for procedures that are directly related to the teeth and the structures directly supporting teeth;

(b) The Medical/Surgical Program is responsible for all dental health procedures performed due to an underlying medical condition (i.e., procedures on or in preparation for treatment of the jaw, tongue, roof of mouth). Such procedures shall be billed using ICD-10, HCPCS and CPT billing codes using the professional (CMS1500, DMAP 505 or 837P) claim format;

(c) D7285, D7286, D7287, D7288 diagnosis codes are reimbursable for all members;

(d) D7990 ancillary code is reimbursable for all members;

(e) All ancillary and diagnosis codes must be dentally necessary.

(f) Alveoloplasty not in conjunction with extractions are reimbursable for members under age 21, and for pregnant individuals (D7320, D7321).

OHAP Straightforward Guideline Note Changes

Plain Language Summary:

Coverage question: Should OHP cover a medical procedure to clip a small piece of tissue under the lip (frenulectomy/frenulotomy) for patients ages 12-21?

Should OHP cover this treatment? Yes, staff propose covering if the patient has receding gums, a condition when gum tissue starts to pull back and wear away from teeth.

Issue: Until 2021, the dental administrative rules contained a limitation of buccal/labial frenulectomy/frenulotomy to children. That portion of the rule has been dropped for unclear reasons. Frenotomy (clipping of the ligament under the tongue) is only covered for newborns with breast feeding difficulties per Guideline Note 139.

The frenulum is a band of tissue in the central portion of the upper lip which serves to provide stability for the upper lip. When this band is short or tight, some practitioners will cut the tissue (frenulectomy) particularly if there is breastfeeding pain, poor latch or other difficulties.

Frenulectomy was last reviewed in November 2022. At that time, the evidence reviewed was regarding frenulectomy as a treatment for breast feeding difficulties or childhood articulation problems. There has not been a review of frenulectomy for adults. A brief literature search by HERC staff found mention of lip tie in adults causing receding gums (gingival recession). The only evidence on frenulectomy found was on breastfeeding, which found that it was not beneficial.

HERC staff recommendation:

1) Modify GN48 as shown below

GUIDELINE NOTE 48, FRENULECTOMY/FRENULOTOMY

Lines 344,661

Labial frenulectomy/frenulotomy (D7961) is included on this line for patients under age 21 in the following situations:

A) When deemed to cause gingival recession
B) When deemed to cause movement of the gingival margin when frenum is placed under tension.
C) Maxillary labial frenulectomy not covered until age 12 and above.

Otherwise, D7961 is included on Line 661.

Section 6.0

BHAP report

BHAP Straightforward Code Change

Plain Language Summary:

Coverage question: Should OHP cover therapy given in a group setting for autism treatment?

Should OHP cover this treatment? Yes, staff recommend that this should be covered.

Issue: Multiple denied claims have been received regarding group psychotherapy for autism spectrum disorder. BHAP recommends that the CPT code for group psychotherapy be added to the autism spectrum disorder line as it could be useful for some people on the autism spectrum.

Multiple denied claims were also seen for residential treatment for autism spectrum disorder. BHAP members felt that residential care was not appropriate for autism spectrum disorder per se. People on the autism spectrum who have another serious mental health issue can assess residential programs for the other serious mental health disorder.

> **90853** Group psychotherapy (other than of a multiple-family group) [appears on most other behavioral health lines]

HERC staff/BHAP recommendation:

1) Add CPT 90853 Group psychotherapy (other than of a multiple-family group) to line 193 AUTISM SPECTRUM DISORDERS

2023 Behavioral Health Related HCPCS Codes

Coverage Question: Should coverage be added for new HCPCS codes regarding coordinated specialty care for early psychosis management?

Question source: HERC staff

Background: CMS issued 2 new HCPCS codes for coordinated specialty care for patient with early psychosis.

1) H2040 Coordinated specialty care, team-based, for first episode psychosis, per month
2) H2041 Coordinated specialty care, team-based, for first episode psychosis, per encounter

From the CMS meeting minutes:
Coordinated Specialty Care - HCP2212301T8X3

Topic/Issue

Request to establish a new HCPCS Level II code to identify Coordinated Specialty Care. Applicant's suggested language: XXXXX, "Coordinated specialty care is an evidence based service delivered by a multidisciplinary team to individuals experiencing a first episode of psychosis"

Summary of Applicant's Submission The National Association of State Mental Health Programs submitted a request to establish a new HCPCS Level II code to identify Coordinated Specialty Care for early or first episode of psychosis (hereafter referred to as CSC). CSC is delivered by a multi-disciplinary team to individuals in the earliest phase of a psychotic illness with the goal of avoiding long-term disability and other costs associated with severe mental health conditions. CSC has been available internationally for several years and in the US for more than 14 years. Following completion of the National Institute of Mental Health-sponsored multi-site Recovery After an Initial Schizophrenia Episode trial, Congress earmarked new funding in the mental health block grant (MHBG) to be provided to the states to stimulate the development of this evidence-based model of care nationally. According to the applicant, while Medicaid funds and some commercial insurers have been billed for individual components of CSC, key components of CSC, such as outreach and engagement, are not captured by existing codes. According to the applicant, providers of CSC have utilized braided funding approaches that involve some combination of the MHBG funds, Medicaid funds, some commercial insurance funds, other state and local funding, as well as philanthropic and other grant dollars to support CSC treatment. This approach is variable by state and region. In addition, much of this braided funding is from discretionary sources and therefore subject to yearly appropriations. According to the applicant, lack of a recognized code specifically developed for CSC has impeded CSC programs' ability to bill insurers for the full service and to expand the coverage of this treatment to other individuals in need. According to the applicant, use of discretionary funds threatens the sustainability of the programs as well as limits the accessibility of CSC treatment since these funds are inadequate to meet the population need. According to the applicant, it has been estimated that 52 percent of costs associated with adequate implementation of CSC is not covered by existing codes/billing mechanisms According to the applicant, without adequate, stable reimbursement, the sustainability – and the associated personal, societal, and financial costs – will continue to be at significant risk. According to the applicant, given the importance of CSC for staving off the

lifelong disability that often accompanies psychotic illnesses, appropriate codes and sustainable insurance payments are critically needed.

CMS Preliminary HCPCS Coding Recommendation We are open to establishing a new code but would like feedback on whether there is overlap with existing HCPCS Level I, Current Procedural Terminology (CPT®) codes and HCPCS Level II codes. We welcome information from the applicant and other insurers, especially individual state Medicaid agencies, to describe how they would approach a unique HCPCS Level II code to identify CSC. 8 For instance, we are currently aware of many HCPCS Level I CPT® codes and HCPCS Level II codes that describe collaborative psychological and behavioral health care services for medical and administrative activity matching such as evaluation, peer specialty services, individual/family/group therapy, and principal care management. Some example codes include, but are not limited to, CPT® codes 90832, 90834, 90837, 90853, 90846, 99212- 99215, 99424-99427, 99484, 99492-99494, and HCPCS Level II codes G0323, G2214, H0036, H0038, H2023, H2024, T1016, T1024, T2022, and T2023. We believe these and other existing codes can be utilized to describe certain coordinated specialty care in different ways. While the applicant suggests that establishing one unique code to recognize coordinated specialty care may be easier for industry tracking purposes, we have observed that when multiple parties are involved in providing aspects of care - particularly when the care includes clinical professionals who customarily bill for services using CPT® codes like 90832 or evaluation and management service codes - that bundled codes can be complex to administer for the multiple parties involved. More specifically, would payers continue to use some or all of these codes and also a code to identify CSC? If so, should a code for CSC be less universal or “bundled” in its description? If the applicant’s suggested description is adopted, would the expectation be that payers describe when to use the code for CSC and when other CPT® codes may be used concurrently for the same patient during a first episode of psychosis? We welcome comments from all interested parties, including state Medicaid agencies and other payers, regarding the request for one bundled code to identify CSC or suggested code language descriptor(s) that would be most useful.

Summary of Public Feedback The National Association of State Mental Health Programs, the applicant, responded to CMS’ published preliminary HCPCS coding recommendation by providing answers to the questions that CMS presented. The commenters generally stated that a unique HCPCS Level II code to identify team-based CSC would help to ensure increased access for individuals with early psychosis and create a streamlined billing experience for insurers and administrators. Many commenters stated that a team-based code would be better utilized by multidisciplinary clinics to identify the entire coordinated service consistent with each payer’s billing guidance. The comments suggested that establishing a new code would also enable public and private insurers to more readily identify CSC in their claims data, facilitate research across the various payers to identify the use of CSC in larger databases, and measure the long-term outcomes and effectiveness of this team-based service. The commenters explained that some public insurers use various combinations of existing codes, such as 90832, H0036, H0038, H0047, T1024, T2022, and T2023, to partially identify services within the CSC model. Many comments stated that while existing codes could be billed for a portion of the provided services such as psychotherapy and medication management, most of these codes are also being used by insurers for other services. According to the comments, the existing codes also do not capture other non-clinical services offered by the CSC team such as education and employment support for the patients. According to the speakers, some public insurers currently use a single code to identify the entire CSC team, while other insurers may also use modifiers or “shadow

claims" to further identify services provided by certain practitioners. 9 Some commenters suggested two HCPCS codes to describe both the monthly and individual encounters. According to the speakers, a monthly case rate is commonly used, but the need for services may vary over time; so, a separate code for an individual encounter rate is helpful when a patient does not meet the minimum requirements to bill a monthly rate. The speakers explained that some insurers may prefer to use only one code for each encounter and may describe each encounter with specific time increments; but the speakers also suggested that existing modifiers would be sufficient for the time increments. The speakers reiterated that two codes for the monthly and individual encounters will allow greater flexibility in the application of various insurance billing policies as well as transparency for the integrity of claims data.

CMS Final HCPCS Coding Decision We appreciate the comments provided in response to CMS' published preliminary recommendation. Based on the information provided in the application and after consideration of the comments received, CMS is finalizing the decision to:
Establish the following two new HCPCS Level II codes:
1. H2040, "Coordinated specialty care, team-based, for first episode psychosis, per month"
2. H2041, "Coordinated specialty care, team-based, for first episode psychosis, per encounter

Current Prioritized List/Coverage status:

CPT 90832, 90834, 90837, 90853, 90846: all behavioral health lines
CPT 99212- 99215, 99424-99427, 99484, 99492-99494: on nearly all lines
HCPCS G0323, G2214: on nearly all lines
HCPCS H0036, H0038, H2023, H2024: all behavioral health lines
HCPCS T1016, T1024, T2022, and T2023: Ancillary

BHAP input:

BHAP recommended coverage for this code, which is designed for case rate care for programs that do early intervention for psychosis (EASA programs). These codes should be added to any line with a psychotic condition. Lynnea Lindsey volunteered to provide HERC staff with the ICD-10-CM codes used by the early psychosis intervention program in her organization. These codes should appear on any line with one of the ICD-10-CM codes on this list.

Per Dr. Lindsey, the most common diagnoses seen in her organization's EASA program

ICD10 Code	Code Description	Current Line(s)
F29	Unspecified psychosis not due to a substance or known physiological condition	275 OTHER PSYCHOTIC DISORDERS
F28	Other psychotic disorder not due to a substance or known physiological condition	275
F41.9	Anxiety disorder, unspecified	411 OVERANXIOUS DISORDER; GENERALIZED ANXIETY DISORDER; ANXIETY DISORDER, UNSPECIFIED
F20.9	Schizophrenia, unspecified	22 SCHIZOPHRENIC DISORDERS
F25.0	Schizoaffective disorder, bipolar type	22

2023 Behavioral Health Related HCPCS Codes

F31.9	Bipolar disorder, unspecified	26 BIPOLAR DISORDERS
F20.81	Schizophreniform disorder	22
F25.1	Schizoaffective disorder, depressive type	22
F32.A	Depression, unspecified	202 DEPRESSION AND OTHER MOOD DISORDERS, MILD OR MODERATE
F31.2	Bipolar disorder, current episode manic severe with psychotic features	26

HERC staff/BHAP recommendation:

1) Add HCPCS H2040 (Coordinated specialty care, team-based, for first episode psychosis, per month) and H2041 (Coordinated specialty care, team-based, for first episode psychosis, per encounter) to the following lines:
    a. 7 MAJOR DEPRESSION, RECURRENT; MAJOR DEPRESSION, SINGLE EPISODE, SEVERE
    b. 22 SCHIZOPHRENIC DISORDERS
    c. 26 BIPOLAR DISORDERS
    d. 277 OTHER PSYCHOTIC DISORDERS
    e. 411 OVERANXIOUS DISORDER; GENERALIZED ANXIETY DISORDER; ANXIETY DISORDER, UNSPECIFIED

Problem Related to Unspecified Psychosocial Circumstances

Plain Language Summary:

Coverage question: Should OHP cover a non-specific mental health and social condition?

Should OHP cover this treatment? Yes, staff suggest covering this as multiple groups in Oregon recommend covering this condition.

Coverage Question: Should Z65.9 (Problem related to unspecified psychosocial circumstance) be added for coverage? If so, should there be limitations on coverage?

Question source: Lydia Chiang, MD, Medical Director, Oregon Pediatric Improvement Partnership (OPIP); 988/Crisis Intervention Team

Background: Oregon Pediatric Improvement Partnership (OPIP) is requesting consideration of ICD-10-CM Z65.9 for coverage, specifically for children who are too young to receive a more definitive diagnosis.

From Dr. Chiang:

> In OPIP's current work with the Social Emotional Health Incentive Measure, we are continuing to learn about important social emotional services young children need to support their development, education, and well-being…As you all know, coverage for these services in the health sector, both in the specialty behavioral health setting and in primary care, requires pairing of CPT codes (such as Health Behavior codes, Psychotherapy codes, Preventive Medicine codes) and a diagnosis, which is tricky in young children birth to five. In some recent conversations we have had with experts in this area, a ICD-10 code was raised that is covered in some other states (California for example) for behavioral health services: Z65.9 Problem related to unspecified psychosocial circumstance. Given Oregon's coverage of EPSDT, I wondered if this diagnosis should be considered for inclusion on the Prioritized list, if not for all ages then at least for young children who might otherwise not have another appropriate Diagnosis that would cover Treatment.

The 988 Crisis intervention team is also requesting that Z65.9 be opened to code for crisis services when there is no pre-existing diagnosis or a diagnosis cannot be made during the crisis encounter.

Previous HSC/HERC reviews:

There are no previous reviews of this code

Problem Related to Unspecified Psychosocial Circumstances

Current Prioritized List/Coverage status:

ICD-10-CM Z65.9 (Problem related to unspecified psychosocial circumstances) is Informational

Most similar codes are Informational (for example, Z65.8 Other specified problems related to psychosocial circumstances). A few codes in this section of the coding manual (for example, Z63.4 Disappearance and death of family member and Z63.8 Other specified problems related to primary support group) are on line 445 ADJUSTMENT DISORDERS

Other payer policies:

1) NY Medicaid
    a. New York State (NYS) Medicaid fee-for-service (FFS) accepts International Classification of Diseases, Tenth Revision (ICD-10) code **"Z65.9"** (problem related to unspecified psychosocial circumstances) as an indication of medical necessity on claims for the psychotherapy services listed below when provided by qualified NYS Medicaid-enrolled providers to NYS Medicaid members under 21 years of age. A diagnosis of **"Z65.9"** is intended for prevention-based services when no other behavioral health diagnosis is present.
        i. Covered services are psychotherapy
2) California Medicaid
    a. Allows use of ICD-10-CM Z65.9 when paired with counseling services
3) United Healthcare
    a. Allows ICD-10-CM Z65.9 to be used only as a secondary diagnosis

BHAP input:

BHAP agreed that these diagnoses should be added to allow OPIP and other early intervention programs to assist kids. It is important to address these issues as early as possible in a child's life to avoid development of mental health issues. BHAP recommended placement of these codes on line 445 ADJUSTMENT DISORDERS. HERC staff was directed to reach out to child psychiatrists and the OPIP program to determine if an age limit should be placed on this diagnosis. The two proposed age limits were 5 and younger and 12 and younger. HERC staff was also directed to reach out to other Medicaid programs for information on other state coverage policies.

HERC staff asked other state Medicaid programs about coverage of these codes and found that coverage varies among state. HERC staff reached out to Dr. Meg Cary, a child psychiatrist, who recommended covering these codes with no age restrictions. After the BHAP meeting, the 988/Crisis services team reached out to HERC about use of Z65.9 for crisis services, which would be for any age person. Based on this, HERC staff are recommending opening this code with no restrictions/guideline.

HERC staff/BHAP recommendation:

1) Add ICD-10-CM Z65.9 (Problem related to unspecified psychosocial circumstances) to line 445 ADJUSTMENT DISORDERS

Transcranial Magnetic Stimulation (TMS) 2023 Review

Plain Language Summary:

Coverage question: TMS uses magnets to create a strong, targeted electric current in certain parts of the brain. which may help improve mental health conditions including depression. Should OHP:
1) Increase the number of treatments allowed?
2) Cover TMS for obsessive compulsive disorder (OCD)?
3) Cover TMS for people under 21 with severe depression?
4) Change the requirements for getting TMS?

Should OHP cover these treatments? Staff recommends:
1) Yes, the number of sessions should be increased by 6.
2) No, there is not any data showing that TMS works for OCD.
3) No, the data is still emerging for this age group.
4) Yes, change the requirements a trial of one medication and a second treatment trial, which could be a medication or therapy.

Coverage questions:

1) Should the number of sessions of transcranial magnetic stimulation (TMS) allowed in GN 102 for treatment-resistant depression be increased?
2) Should TMS be covered for obsessive compulsive disorder (OCD)?
3) Should TMS be covered for adolescents with major depressive disorder?
4) Should the requirements for qualification for TMS (failure of 2 trials of psychoactive medications and a trial of psychotherapy) be modified?

Question sources:

1) Juliana Ayers, PMHMP and Chad Brown MD, community TMS providers
2) John Bischoff, psychiatrist, CareOregon Behavioral Health Medical Director and BHAP member
3) John Bischoff
4) Meg Cary, MD MPH, OHA medical director, John Bischoff

Background: Transcranial magnetic stimulation (TMS) is a neurostimulation technique that uses a magnetic field to induce a strong and focused electrical current that is delivered to specific regions of the brain to treat “treatment resistant” depression. HERC approved coverage initially for TMS as part of a coverage guidance in 2012. The TMS guideline was reviewed in 2020 and additional criteria and limits were placed on TMS due to updated trusted evidence source reviews (CADTH 2019, NICE 2015, Washington HTA 2014). One of the limits added to the guideline was a limit of 30 sessions (5 sessions a week for 6 weeks).

Transcranial Magnetic Stimulation (TMS) 2023 Review

Dr. Brown and Ms. Ayers are requesting a review of the visit limit numbers.
From Ms. Ayers:

> Our dTMS [deep Transcranial Magnetic Stimulation] coil is a unique coil that is different from the figure 8 coil used in repetitive TMS. It is designed to go deeper into the cortical tissue as well as target a larger area of the dorsolateral prefrontal cortex, the area of the brain theorized to be metabolically underactive in depression. The dTMS treatment protocol is 20 active treatments followed by 2 treatments a week for 3 months, for a total of 44 treatments. Note in the attached study that patients who have not responded to dTMS during the active phase, achieved remission or response during the 3 month taper phase. We have seen this as well in our clinic. We also find that the extended taper enhances durability of response. We have a lot of patients with chronic depression and a high stress load with multiple determinants of social health who seem to be more resilient to stress and relapse with this protocol.

Previous reviews of TMS have only been for treatment resistant depression. TMS recently received FDA approval for treatment of OCD and Dr. Bischof is requesting evaluation of possible coverage for that indication.

Previous reviews of TMS have only focused on adult populations (aged 18 and older). Dr. Bischoff requested a review of TMS for adolescents based on emerging safety and efficacy evidence in this population.

Dr. Cary requested consideration of possibly reducing the number of required psychotherapy sessions required prior to TMS therapy. She felt weekly therapy for at least 6 weeks is a hardship for the OHP population due to lack of access to mental health care, need for time off work, etc.

Dr. Bischof requested a review of the current required number and specificity of medication trials required prior to TMS therapy. The FDA approval for TMS requires failure of one antidepressant medication, while our current guideline requires failure of two medications.

Previous HSC/HERC reviews:

See above for comments on the 2020 review and 2012 coverage guidance review

Current Prioritized List/Coverage status:

GUIDELINE NOTE 102, REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION

Line 7

Repetitive transcranial magnetic stimulation (CPT 90867-90869) is included on this line only when ALL of the following criteria are met:

A) The patient has a confirmed diagnosis of severe major depressive disorder based on standardized rating scales, AND
B) The patient has treatment resistant depression as evidenced by BOTH of the following:
    1. Ongoing symptoms despite treatment with at least 2 psychopharmacologic regimens each used for 8 weeks unless not tolerated or contraindicated, AND

2. Failure of a trial of psychotherapy conducted for a minimum duration of 6 weeks at least 1 time a week with no improvement in depressive symptoms as documented by standardized rating scales; AND

C) The patient does not have psychosis, acute suicidal risk, catatonia, significantly impaired essential function, or other condition for which electroconvulsive therapy (ECT) would be clinically superior to TMS; AND
D) The patient has no contraindications to rTMS such as implanted devices in or around the head, increased risk of seizure, etc; AND
E) The therapy is administered by an FDA approved device in accordance to labeled indications; AND
F) The patient is 18 years of age or older.

Repetitive transcranial magnetic stimulation is covered for a maximum of 30 sessions (once a day, up to 5 times per week for 6 weeks) for initial treatment. Repeat treatment may be covered if the patient responded to the initial treatment (defined as at least 50 percent reduction in depression score on standardized rating scale) and at least 3 months have elapsed since the initial treatment.

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

Evidence:

Deep TMS

1) **Hung 2020**, Systematic review and meta-analysis of efficacy of deep transcranial magnetic stimulation for treatment resistant depression
    a. N=15 studies
        i. 3 RCTs (N=417 patients)
        ii. 12 uncontrolled clinical trials (N=284 patients)
        iii. Treatment duration in RCTs: 4 weeks
        iv. Treatment duration in uncontrolled trials:
            1. 10 studies: 4 weeks
            2. 1 study: 4-6 weeks
            3. 1 study: 5 weeks
            4. 1 study: 12 weeks (Levkowitz 2015)
    b. For symptom load in pre- to post-test studies, dTMS significantly improved depressive symptoms (Hedges' g = −1.323, 95% CI = −1.651 to −0.995, p < .001, k = 15, n = 701) and anxiety symptoms (Hedges' g = −1.282, 95% CI = −1.514 to −1.051, p < .001, k = 8, n = 188)
    c. For depression treatment, there was evidence of publication bias (Egger's regression test, p = .02) and significant heterogeneity (I 2 = 87.5%, p < .001)
    d. For depression severity, RCTs had smaller effects than non-RCTs (RCT: Hedges' g = −0.756, 95% CI = −1.600 to 0.087, p = .079, k = 3, n = 417; non-RCT: Hedges' g = −1.461, 95% CI = −1.789 to −1.133, p < .001, k = 12, n = 284)
    e. Studies using combined antidepressant medications showed larger antidepressant effect than those not using combined antidepressant medications (antidepressant (+):

Hedges' g = −1.429, 95% CI = −1.767 to −1.091, p < .001, k = 12, n = 459; antidepressant (−): Hedges' g = −0.866, 95% CI = −1.589 to −0.144, p = .019, k = 3, n = 242)

f. The response rate in the dTMS group was 47.8% (213/446), while that in the sham group was 25.6% (56/219). The OR of response rate in the dTMS group was 2.883 (95% CI = 2.007 to 4.142, p < .001). The remission rate in the dTMS group was 36.6% (140/383), while that in the sham group was 14.8% (31/209). The OR of remission rate in the dTMS group was 2.060 (95% CI = 1.676 to 2.531, p < .001)
g. With regard to the response rate of patients with depression, the beneficial effect of dTMS persisted in patients using combined anti-depressant medications (Hedges' g = 3.106, 95% CI = 2.193 to 4.399, p < .001, k = 10, n = 430); however, the effect was not observed in those not using antidepressant medications (Hedges' g = 2.228, 95% CI = 0.830 to 5.983, p = .112, k = 3, n = 242)
h. Only patients using combined antidepressant medications reached clinical significance (Hedges' g = 2.144, 95% CI = 1.804 to 2.547, p < .001, k = 10, n = 430); however, the beneficial effect of dTMS disappeared in those not using combined antidepressant medications (Hedges' g = 1.981, 95% CI = 0.923 to 4.251, p = .079, k = 3, n = 242)
i. Conclusion: Although the response and remission rates of the dTMS group were high, only studies using both dTMS and antidepressant medications achieved significance. dTMS is a safe and effective intervention in patients with TRD.

TMS for OCD

1) **Washington HTA 2023,** Transcranial Magnetic Stimulation for Treatment of Selected Behavioral Disorders https://www.hca.wa.gov/assets/program/TMS-final-report.pdf
    a. Seven RCTs reported clinical response, defined as a decrease in Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score of 25% or more; pooled RR 1.96 (95% CI, 0.94 to 4.09; 281 participants; I 2=47.1%); ARD 155 more clinical responses per 1,000 participants (95% CI, from 9 fewer to 487 more) for TMS compared to sham. (SOE: Low, favor TMS)
    b. Nine RCTs reported using Y-BOCS. Change in severity of OCD symptoms from the Y-BOCS was the primary outcome in all but 1 study. Results were mixed with 5 studies reporting that TMS was associated with symptom severity improvement (statistically significant in 4 studies), 1 study favoring sham (non-significant) and 3 studies that did not report direction of effect of TMS treatment on OCD symptom severity. (SOE: Low, favor TMS)
    c. Eight RCTs reported on AEs. There were no differences in any AEs or severe AEs between groups. Headache and localized scalp pain were the most frequently reported side effects across groups. (SOE: Low, no difference)
2) **Fitzimmons 2022,** systematic review and meta-analysis of TMS for OCD
    a. N=21 RCTs (662 patients)
    b. Evidence base included mostly small studies, with only a few studies using similar protocols, giving a sparse network. Studies were heterogeneous, and a risk of publication bias was found.
    c. For post-treatment Yale-Brown Obsessive Compulsive Scale (YBOCS), Hedges' g=− 0.502 [95%CI=− 0.708, − 0.296], indicating a significantly greater improvement in YBOCS following active rTMS than following sham rTMS. Clinically, this translates to four points more decrease in the YBOCS severity score when using rTMS compared with sham rTMS
        i. Note: Clinically meaningful change in the Y-BOCS: patients experience a 25% decrease in a Y-BOCS score as mild to moderate improvement, and decrease of 35-50% as moderate to marked

   d. Conclusion: rTMS is efficacious compared with sham across three different rTMS protocols (HF bilateral dlPFC, LF preSMA, and LF right dlPFC) for the treatment of OCD.

3) **NICE 2020**, TMS for OCD https://www.nice.org.uk/guidance/ipg676/resources/transcranial-magnetic-stimulation-for-obsessivecompulsive-disorder-pdf-1899874288332997
   a. Evidence on the safety of transcranial magnetic stimulation for obsessive-compulsive disorder raises no major safety concerns. However, evidence on its efficacy is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research.
   b. The evidence included 1 systematic review and meta-analysis, 7 randomized controlled trials (1 of which is also included in the systematic review), 1 case series and 1 review of seizures reported after deep rTMS.
   c. In a meta-analysis of 18 randomized controlled trials (RCTs) including 484 patients who had active or sham low- or high-frequency rTMS, active rTMS was statistically significantly superior to sham rTMS in reducing the Yale-Brown Obsessive Compulsive Scale score (g=0.79, 95% confidence interval [CI] 0.43 to 1.15, p<0.001) [Rehn 2018 below]
   d. 7 RCTs (N=320 patients)
      i. RCT with 99 patients: Y-BOCS score decreased by 6.5 (95% CI 4.3 to 8.7) and 4.1 (95% CI 1.9 to 6.2) points respectively at 4-week follow up (p=0.03).
      ii. In an RCT of 41 patients who had high-frequency, low-frequency or sham deep TMS, the response rates (30% or greater reduction in Y-BOCS score relative to baseline) were 44% (7/16) in the high-frequency deep TMS group and 7% (1/14) in the sham group at the end of treatment (p<0.05)
      iii. In an RCT of 40 patients who had active or sham low-frequency rTMS, the percentage reduction in Y-BOCS scores was 24% in the active group and 15% in the sham group (p=0.27)
      iv. In an RCT of 57 patients who had active or sham low-frequency rTMS with SSRIs, the mean Y-BOCS scores reduced from 17.2 at baseline to 11.7 at the end of 4 weeks of treatment in the active rTMS group (p<0.01).
      v. In an RCT of 50 patients who had low-frequency rTMS or antipsychotic augmentation, the mean Y-BOCS scores reduced from 30.16 to 20.92 and from 31.44 to 25.56 respectively at the end of treatment
      vi. In an RCT of 60 patients who had high-frequency rTMS as add-on treatment, high-frequency rTMS as monotherapy or sham rTMS (also included in the meta-analysis), a good response was reported for 55% (11/20), 25% (5/20) and 5% (1/20) respectively (p=0.07 between sham and monotherapy; p=0.05 between monotherapy and add-on treatment; p=0.006 between sham and add-on treatment).
      vii. In an RCT of 30 patients who had theta-burst rTMS, there was no statistically significant difference in responder rates (defined as at least 25% decrease on the Y-BOCS) between those who had active treatment and those who had sham treatment (28% compared with 36% at both 6 and 12 week follow-up, p=0.686)

TMS for adolescents

1) **Washington HTA 2023,** Transcranial Magnetic Stimulation for Treatment of Selected Behavioral Disorders

   a. One qualifying study on adolescents was found. The study in adolescents was conducted in individuals aged 12 to 21 years and was funded entirely by industry. Eligible participants had MDD symptoms greater than 4 weeks and less than 3 years and had to report intolerance to at least 4 prior trials of medications. The mean age of participants was 17 years. Participants were randomized to HF-rTMS or sham and treated daily, 5 times a week, for 6 weeks. No differences in remission, response, change in symptom severity over baseline (as measured by HAMD24 and CGI-S), suicidality, or other SAEs were observed between groups. Specific AEs reported included headache, eye pain, nausea, and facial twitching

2) **Sigrist 2022**, systematic review and meta-analysis of TMS for treatment of adolescent depression
   a. N=10 studies (247 patients), including 2 RCTs and 8 non-controlled trials
      i. Mean age 17.45 years
      ii. Sample sizes ranged from N=8 to N=48 participants
   b. Synthesis of all 10 studies examining pre- to post-treatment change in depression scores resulted in a significant pooled effect size estimate (pooled SMCC=2.04, 95% CI [1.46; 2.61], SE=0.29, p<0.001)
   c. Existing studies exhibit methodological shortcomings, including small-study effects and lack of control group, blinding, and randomization—compromising the credibility of the present results. To date, two randomized controlled trials on TMS in adolescent depression have been published, and the only large-scale randomized trial suggests TMS is not more effective than sham stimulation.

Study definitions of "treatment resistant depression"

1) **Washington HTA 2023,** Transcranial Magnetic Stimulation for Treatment of Selected Behavioral Disorders
   a. N=36 RCTs
      i. 28 studies defined treatment resistance as failure of at least 2 medications.
      ii. Six studies defined treatment resistance as failure of at least 1 medication
      iii. One study defined treatment resistance as failure of at least 3 medications
      iv. One study defined treatment resistance as failure of at least 4 medications.
      v. No mention of failure of psychotherapy

Submitted literature:

dTMS

1) Levkowitz 2015
   a. Included in the Hung 2020 systematic review
2) Yip 2017
   a. Subgroup analysis of the Levkowitz 2015 trial

Expert guidelines:

TMS for OCD

1) **Fineberg 2020**, Clinical advances in obsessive-compulsive disorder: a position statement by the International College of Obsessive-Compulsive Spectrum Disorders

a. To summarize, LF-rTMS delivered over the SMA (with figure-8 coil) and HF-deep-rTMS over the dorsomedial prefrontal cortex/anterior cingulate cortex (with H7 coil) appear promising interventions in treatment-resistant OCD. There is a pressing need for large replication studies and evaluation of long-term effects/maintenance protocols. The evidence for tDCS is highly preliminary and further exploratory studies are encouraged.

Other payer policies:

Number of TMS sessions

1) CMS 2019, National coverage policy for transcranial magnetic stimulation
    a. TMS is reasonable and necessary for up to 20 visits over a 4-week period followed by five visits for tapering for those in remission. For those who show at least 25% improvement by means of the standard tests for depression, the therapy may be continued for an additional 2 weeks (an additional 10 visits) with an additional 6 visits for tapering.
    b. Retreatment may be considered for patients who met the guidelines for initial treatment and subsequently developed relapse of depressive symptoms if the patient responded to prior treatments as evidenced by a greater than 50% improvement in standard rating scale measurements for depressive symptoms or if there was a relapse after remission (e.g., (GDS), PHQ-9, BDI, HAM-D, MADRS, QIDS or IDS-SR score). A repeat treatment program is allowed as above.
    c. Maintenance therapy is considered experimental/investigational and therefore non-covered as not medically reasonable and necessary.
2) Aetna 2023
    a. Treatment consists of a maximum of 30 sessions (5 days a week for 6 weeks) plus 6 tapering sessions (6 sessions over three weeks). **Notes**: Treatments beyond 36 sessions (e.g., 30 treatment sessions followed by 6 tapering sessions) may be reviewed for medical necessity. There is a lack of evidence of the effectiveness of additional sessions beyond 36 to treat "late responders", to solidify response, or to attain remission.
3) Premara BCBS 2023
    a. A full intensive course of standard/conventional repetitive transcranial magnetic stimulation or theta burst stimulation
        i. A course of 30 treatments over 6-7 weeks, at a frequency of one treatment daily 4-5 days per week, with an optional 6 additional treatments for a taper over 3 weeks (3 treatments on separate days in the first week, 2 treatments on separate days in the second week, and 1 treatment in the third week), for a total of 30 or 36 treatments.
    b. A full intensive course of deep TMS
        i. A course of 20 treatments over 4 weeks, at a frequency of one treatment daily 5 days per week, called the intensive phase, followed by a course of 2 treatments weekly on separate days over 10-12 weeks, called the continuation phase, for a total of 40-44 treatments; OR
        ii. A course of 30 treatments over 6-7 weeks, at a frequency of one treatment daily 4-5 days per week, with an optional 6 additional treatments for a taper over 3 weeks (3 treatments on separate days in the first week, 2 treatments on

separate days in the second week, and 1 treatment in the third week), for a total of 30 or 36 treatments.

4) United Health Care 2023
    a. TMS is considered reasonable and necessary for up to 30 treatment sessions, followed by 6 tapered treatments
5) Regence BCBS 2023
    a. Transcranial magnetic stimulation (TMS) of the brain may be considered medically necessary as a treatment of major depressive disorder when either of the following criteria are met:
        i. A. As initial treatment of a depressive episode (up to 36 treatment sessions, including tapering)
6) MODA 2022
    a. Allow a total of 36 sessions of TMS
    b. A typical course of TMS is 5 days a week for 6 weeks (total of 30 sessions), followed by a 3 week taper of 3 TMS treatments in week 1, 2 TMS treatments the next week, and 1 TMS treatment in the last week (36 treatments total).
    c. The role of follow-up or maintenance treatment has not been established in the literature and there is not yet a generally accepted protocol for maintenance treatment

Other Medicaid program coverage

1) Washington Medicaid 2023
    a. Limited to 30 sessions for major depressive disorder
2) Vermont Medicaid
    a. TMS is administered by a U.S. Food and Drug Administration (FDA) cleared device for the treatment of MDD according to specified stimulation parameters, 30 sessions over a 7-week period followed by a 3-week taper of 3 TMS treatments in 1 week, 2 TMS treatments the next week, and 1 TMS treatment in the last week
3) Montana Medicaid
    a. For initial treatment: maximum 30 visits (up to 5 times per week) over a 6 to 7-week period with a 2-week taper (6 taper sessions)
4) Iowa Medicaid
    a. Once approved, a course of 30 sessions (typically 5 days a week for 6 weeks) followed by 6 sessions for tapering therapy over the next several weeks.

TMS for OCD

1) CMS 2022
    a. TMS is reasonable and necessary for OCD for a minimum of 29 visits over a 6 week period. Extensions in 2 to 4 week increments will be cleared based on clinical need with evidence of response from the first 29 sessions. If patients cannot come in 5 days a week, treatments may be administered 3 days a week over a longer period of time
2) Premara BCBS
    a. Covers TMS for OCD for individuals 18 and older with moderate to severe OCD who have fails trails of at least 3 medications
3) Regence BCBS
    a. Considers TMS for OCD to be investigational
4) United Healthcare 2021
    a. Considers TMS for OCD to be investigational

5) Cigna 2023
    a. Covers TMS (30-36 sessions) for OCD for adults who have failed two or more trials of medications and a trial of psychotherapy
6) Washington Medicaid 2023
    a. TMS for treatment of obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD), post-traumatic stress disorder (PTSD), smoking cessation, and substance use disorder (SUD) are not covered.
7) Aetna 2023
    a. Considers TMS for OCD to be investigational

TMS for adolescent depression

1) Washington Medicaid 2023
    a. Does not cover TMS for adolescents
2) Premara BCBS
    a. Covers TMS for depression for adolescents aged 15-18
3) United Health care
    a. Does not cover TMS for adolescents
4) Regence BCBS
    a. Patients must be 18 years or older
5) Aetna 2023
    a. Patients must be 18 years or older

Treatment required prior to approval of TMS

1) Washington Medicaid 2023
    a. Failure of at least 2 different antidepressant medications from at least 2 separate classes at maximum tolerated dose for 4-12 weeks in separate trials
    b. No requirement for psychotherapy
2) Aetna 2023
    a. Inadequate response to two antidepressants from at least 2 different classes having different mechanisms of action (see Appendix) at the maximally tolerated labeled dose, each used for at least 8 weeks
    b. No requirement for psychotherapy
3) Cigna 2023
    a. Failure of two or more trials of antidepressant medications from two separate classes of antidepressant medications. A failed trial is defined as EITHER of the following:
        i. use of an antidepressant medication at adequate therapeutic doses for at least four weeks with no significant reduction in depressive symptoms
        ii. use of an antidepressant medication with documented intolerance or medical contraindication
    b. an adequate trial of an evidence-based psychotherapy known to be effective in the treatment of major depressive disorder, without significant improvement in depressive symptoms
4) United Healthcare 2023
    a. Resistance to treatment with psychopharmacologic agents as evidenced by a lack of a clinically significant response to 2 trials of psychopharmacologic agents in the current depressive episode from at least 2 different agent classes
    b. No requirement for psychotherapy

Transcranial Magnetic Stimulation (TMS) 2023 Review

5) CMS 2019, National coverage policy for transcranial magnetic stimulation
    a. The patient has demonstrated a failure of one or more trials of a pharmacological medication and/or demonstrates an intolerance to psychopharmacologic medications as defined in the definition section above
        i. **Failure of a trial of a pharmacological agent:** The failure of one or more psychopharmacological medications that are administered at both an adequate dose and adequate duration that are consistent with the FDA label and with a duration that would elicit a favorable response
6) Regence BCBS 2023
    a. Symptoms are ongoing despite treatment with the following psychopharmacologic regimens, and each has been ineffective, not tolerated (as evidenced by distinct side effects), or is contraindicated (see Policy Guidelines):
        i. Either of the following:
            1. At least 3 antidepressant medications from at least 2 different classes in separate trials; or
            2. At least 2 different antidepressant medications from at least 2 different classes in separate trials, plus failure with the addition of an augmenting agent to at least one of the failed antidepressants; and
            3. At least four weeks' duration for one or more of the antidepressant agents (unless none of the agents was tolerated)
    b. Failure of a trial of a psychotherapy (see Policy Guidelines) known to be effective in the treatment of major depressive disorder, when both of the following criteria are met (a. - b.):
        i. a. Documentation is submitted showing that psychotherapy was conducted for a minimum duration of 6 weeks at least 1 time per week; and
        ii. b. No significant improvement in depressive symptoms has occurred, as documented in the clinical records

BHAP input:

Number of covered sessions: there was general agreement that adding 6 taper sessions was a desirable change. Testimony was heard from Schuler Ellis, a psychiatric nurse practitioner who providers TMS therapy, that up to 56 sessions should be considered for late responder patients. BHAP members felt that the addition of the 6 taper sessions was sufficient.

Adding coverage for TMS for OCD: Mr. Ellis testified that his personal experience is that TMS provides a good response for OCD, with about a 30% reduction in patients who do respond. OCD is difficult to treat, medications are not as helpful. BHAP members were not in favor of adding coverage for OCD based on the lack of consistent data showing a benefit.

Adding coverage for adolescents: no BHAP member recommended this, and Mr. Ellis testified that he agreed that the adolescent data is emerging, and agrees with not covering at this time.

Requirements before TMS approval: BHAP members were split on whether there was sufficient access to psychotherapy currently in Oregon to continue to require a trial of psychotherapy prior to TMS. There was also question about whether the current requirement of 6 sessions even constitutes a realistic trial of psychotherapy. Robbins stated that in her opinion, TMS should be first line treatment with no requirements. The group noted that TMS was only FDA approved for "treatment resistant

depression." There was vigorous discussion about what constitutes "treatment resistant depression." Mr. Ellis testified that most private payer policies have removed the requirement for a trial of psychotherapy. The final recommendation of the BHAP was to modify the guideline to require at least one medication trial and a second treatment trial, which could either be medication or psychotherapy. This reflects that psychotherapy is equally effective to medications and addresses some member concerns about medication side effects.

Additional public comment: an audience member noted that there are multiple versions of TMS now being used, and recommended that "repetitive" be removed from the guideline title to reflect this.

Transcranial Magnetic Stimulation (TMS) 2023 Review

HERC staff summary:

Number of sessions: The large majority of studies on TMS were 4 weeks long (20 sessions). Major insurers allow 30 treatments for TMS, with many allowing 6 additional treatments as a taper. HERC staff literature searches for evidence on TMS tapering found no studies specifically on the benefit of an additional 6 sessions to taper TMS vs the standard 30 sessions used in most clinical trials. However, it appears to be standard among private insurers and other state Medicaid programs to allow 6 tapering sessions. However, Washington Medicaid's evidence-based policy only allows 30 sessions. BHAP recommended adding 6 taper sessions as this is what is standard in the community treatment setting.

Coverage of TMS for OCD: The evidence for TMS as a treatment for OCD is limited. A recent Washington HTA report found mixed results. The clinical response found in 7 RCTs was not clinically significant when analyzed for clinically meaningful change in the Yale-Brown Obsessive-Compulsive Scale (defined as a decrease of 25% or more). A recent systematic review and meta-analysis found that the evidence base included mostly small heterogenous studies and a risk of publication bias was found. Two trusted evidence base sources (Washington HTA and NICE) recently reviewed TMS for OCD and did not find sufficient evidence to cover this indication. Other insurer coverage of TMS for OCD is mixed. HERC staff and BHAP recommend against adding coverage of TMS for OCD.

Coverage of TMS for adolescents: The evidence for TMS as a treatment for depression for adolescents is limited. The only large scale RCT published did not find evidence of effectiveness. A recently trusted evidence source review (Washington HTA) did not find sufficient evidence of effectiveness to cover TMS for adolescents. Most other insurers do not cover TMS for people less than 18 years of age. HERC staff and BHAP recommend against adding coverage of TMS for adolescents.

Requirements to qualify for TMS: Most major insurers do not require a trial and failure of psychotherapy prior to approval of TMS. The studies on TMS did not include failure of psychotherapy in their definition of "treatment resistant depression." The studies on TMS overwhelmingly defined "treatment resistant depression" as a failure to respond to at least 2 medications. The FDA only requires failure of one medication. All other insurers surveyed require trial and failure of antidepressant medications prior to TMS therapy, with the majority requiring a trial of at least 2 medications. BHAP recommended changing the current requirements to one medication trial and a second trial of either another medication or psychotherapy.

HERC staff/BHAP recommendations:

1) Modify GN102 as shown below

GUIDELINE NOTE 102, ~~REPETITIVE~~ TRANSCRANIAL MAGNETIC STIMULATION

Line 7

~~Repetitive~~ ~~t~~Transcranial magnetic stimulation (CPT 90867-90869) is included on this line only when ALL of the following criteria are met:

A) The patient has a confirmed diagnosis of severe major depressive disorder based on standardized rating scales, AND

B) The patient has treatment resistant depression as evidenced by ~~BOTH of the following:~~

1. Ongoing symptoms despite treatment with one psychopharmacologic regimen ~~each used for 8 weeks~~ administered at both an adequate dose and adequate duration that

are consistent with the FDA label and with a duration that would elicit a favorable response unless not tolerated or contraindicated, AND

2. Failure of a trial of EITHER a second psychoactive medication as above OR psychotherapy conducted for a minimum duration of 6 weeks at least 1 time a week with no improvement in depressive symptoms as documented by standardized rating scales; AND

C) The patient does not have psychosis, acute suicidal risk, catatonia, significantly impaired essential function, or other condition for which electroconvulsive therapy (ECT) would be clinically superior to TMS; AND
D) The patient has no contraindications to rTMS such as implanted devices in or around the head, increased risk of seizure, etc; AND
E) The therapy is administered by an FDA approved device in accordance to labeled indications; AND
F) The patient is 18 years of age or older.

Repetitive transcranial magnetic stimulation is covered for a maximum of 30 sessions (once a day, up to 5 times per week for 6 weeks) for initial treatment, followed by up to 6 taper treatments. Repeat treatment may be covered if the patient responded to the initial treatment (defined as at least 50 percent reduction in depression score on standardized rating scale) and at least 3 months have elapsed since the initial treatment.

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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Efficacy and tolerability of deep transcranial magnetic stimulation for treatment-resistant depression: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Brain stimulation
Deep transcranial magnetic stimulation
Depression
Treatment-resistant
Meta-analysis
dTMS

ABSTRACT

Objectives: This study aimed to investigate the efficacy of deep transcranial magnetic stimulation (dTMS) for treatment-resistant depression (TRD).

Methods: This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. PubMed, Medline, PsycINFO, Embase, and Cochrane Library were systematically searched from the time of their inception until July 17, 2019. Data were pooled using a random-effects model. Primary outcomes were mean change of depression and anxiety severity. Secondary outcomes were response and remission rate of depression.

Results: Fifteen studies including three randomized controlled trials (RCTs) (n = 417, mean age: 50.6 years) and twelve uncontrolled clinical trials (n = 284, mean age: 46.4 years) were included. dTMS significantly improved the depressive (Hedges' g = −1.323, 95% CI = −1.651 to −0.995, p < .001) and anxiety symptoms (Hedges' g = −1.282, 95% CI = −1.514 to −1.051, p < .001) in patients with TRD. Subgroup analysis showed that non-RCTs had a larger effect size than RCTs (−1.461 vs −0.756) on depression severity. Although the response and remission rates of the dTMS group were high, only studies using both dTMS and antidepressant medications achieved significance. The anxiolytic effect of dTMS was more heterogeneous, and the results were obtained mainly from non-RCTs. Importantly, the dTMS group showed favorable tolerability without major adverse events.

Conclusions: dTMS is a safe and effective intervention in patients with TRD. Studies combining dTMS and antidepressant medications seemed to show greater therapeutic effects. Future studies are needed to address the interaction effect of dTMS with different classes of antidepressant medications.

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Washington State Health Care Authority

Health Technology Clinical Committee
FINAL Findings and Decision

Topic: Transcranial Magnetic Stimulation (TMS)
Meeting date: March 17, 2023
Final adoption: June 23, 2023

Number and coverage topic:
20230317A – Transcranial Magnetic Stimulation for the Treatment of Selected Conditions

HTCC coverage determination:
TMS for treatment resistant major depressive disorder (MDD) in adult patients (age 18 or older) is a **covered benefit with conditions**.

TMS for treatment of obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD), post-traumatic stress disorder (PTSD), smoking cessation, and substance use disorder (SUD) are **not covered**.

HTCC reimbursement determination:
Limitations of coverage:
Initial treatment (up to 30 treatment sessions) is covered when ALL of the following criteria are met:

1. Failure of at least 2 different antidepressant medications from at least 2 separate classes at maximum tolerated dose for 4-12 weeks in separate trials, and
2. TMS is administered according to an FDA-cleared protocol.

Repeat TMS for MDD (up to 30 treatment sessions):

1. All of the above criteria have been met,
2. Improvement in symptoms is maintained for at least 6 weeks following initial treatment session, and
3. Individual has shown evidence of 30% or more improvement on the Hamilton Depression Rating Scale, **OR** a minimally clinically important difference on a validated scale for depression, with most recent TMS treatment.

Notes:

- Concurrent psychotherapy and/or antidepressant medication treatment is allowable as appropriate.
- Determination does not apply to age 17 and younger.

Related documents:

- Final key questions
- Final evidence report
- Meeting materials and transcript

Agency contact information:

Agency	Phone Number
Labor and Industries	1-800-547-8367

Public and School Employees Health Plan	1-800-200-1004
Washington State Medicaid	1-800-562-3022

HTCC coverage vote and formal action:

Committee decision

Based on the deliberations of key health outcomes, the committee decided that it had the most complete information: a comprehensive and current evidence report, public comments, and state agency utilization information. The committee discussed and voted separately on the evidence for the use of TMS for MDD, OCD, GAD, PTSD, smoking cessation, and SUD. The committee decided that the current evidence on TMS for MDD is sufficient to determine coverage with conditions. The committee considered the evidence, public comment and expert input, and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Based on these findings, the committee voted to cover with conditions TMS for MDD. Separately, the committee voted not to cover TMS for OCD, GAD, PTSD, smoking cessation, and SUD.

	Not covered	Covered under certain conditions	Covered unconditionally
TMS for MDD	0	9	0
TMS for OCD	9	0	0
TMS for GAD	9	0	0
TMS for PTSD	9	0	0
TMS for smoking cessation	9	0	0
TMS for SUD	9	0	0

Discussion

The committee reviewed and discussed the available studies for use of TMS for MDD, OCD, GAD, PTSD, smoking cessation, and SUD. Conditions for coverage were discussed, drafted, and voted on. All committee members present supported the conditions of coverage of TMS for MDD. Details of study design, inclusion criteria, outcomes, cost, cost-effectiveness, and other factors affecting study quality were discussed as well as clinical application.

Decision

TMS for treatment resistant **Major Depression Disorder (MDD)** in adult patients (age 18 or older) is a covered benefit with conditions:

Initial treatment (up to 30 treatment sessions) is covered when ALL of the following criteria are met:

1. Failure of at least 2 different antidepressant medications from at least 2 separate classes at maximum tolerated dose for 4-12 weeks in separate trials; and
2. TMS is administered according to an FDA-cleared protocol.

Repeat TMS for MDD (up to 30 treatment sessions):

1. All of the above criteria have been met, and
2. Individual has shown evidence of 30% or more improvement, or a minimally clinically important difference, on a validated scale for depression, with most recent TMS treatment, and
3. Improvement in symptoms is maintained for at least 6 weeks.

Notes:
Concurrent psychotherapy and/or antidepressant medication treatment is allowable as appropriate. Determination does not apply to age 17 and younger.

TMS is not covered for any age group for the treatment of other behavioral health disorders, including:

- Obsessive-compulsive disorder (OCD);
- Generalized anxiety disorder (GAD);
- Post-traumatic stress disorder (PTSD);
- Smoking cessation; and
- Substance use disorder (SUD)

Action

The committee checked for availability of a Centers for Medicare and Medicaid Services (CMS) national coverage decision (NCD). Based on the information provided in the systematic review, there is no NCD for transcranial magnetic stimulation.

The committee discussed clinical guidelines identified from the following organizations:

- Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS) (European Expert Panel) (2020)
- French Recommendations from experts, the French Association for Biological Psychiatry and Neuropsychopharmacology and the foundation FondaMental *Clinical guidelines for the management of treatment-resistant depression* (2019)
- National Network of Depression Centers rTMS Task Group and the American Psychiatric Association Council on Research Task Force on Novel Biomarkers and Treatments *Consensus Recommendations for the Clinical Application of Repetitive Transcranial Magnetic Stimulation in the Treatment of Depression* (2018)
- Canadian Network for Mood and Anxiety Treatments (CANMAT) *2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder* (2016)
- National Institute of Health and Care Excellence (NICE) *Repetitive transcranial magnetic stimulation for depression* (2015)
- National Institute of Health and Care Excellence (NICE) *Repetitive transcranial magnetic stimulation for obsessive-compulsive disorder* (2020)
- European Expert Panel *Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS)* (2020)
- Canadian Anxiety Guidelines Initiative Group *Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders* (2014)

The recommendations of the guidelines vary. The committee's determination is consistent with the noted guidelines.

HTA staff will prepare a findings and decision document on use of transcranial magnetic stimulation for the treatment of selected conditions for public comment to be followed by consideration for final approval at the next committee meeting.

Health Technology Clinical Committee Authority:

Washington State's legislature believes it is important to use a science-based, clinician-centered approach for difficult and important health care benefit decisions. Pursuant to chapter 70.14 RCW, the legislature has directed the Washington State Health Care Authority (HCA), through its Health Technology Assessment (HTA) program, to engage in an evaluation process that gathers and assesses the quality of the latest medical evidence using a scientific research company that takes public input at all stages.

Pursuant to RCW 70.14.110, a Health Technology Clinical Committee (HTCC) composed of eleven independent health care professionals reviews all the information and renders a decision at an open public meeting. The Washington State HTCC determines how selected health technologies are covered by several state agencies (RCW 70.14.080-140). These technologies may include medical or surgical devices and procedures, medical equipment, and diagnostic tests. HTCC bases its decisions on evidence of the technology's safety, efficacy, and cost effectiveness. Participating state agencies are required to comply with the decisions of the HTCC. HTCC decisions may be re-reviewed at the determination of the HCA Director.

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Review article

Repetitive transcranial magnetic stimulation for obsessive-compulsive disorder: A systematic review and pairwise/network meta-analysis

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ARTICLE INFO

Keywords:
Repetitive transcranial magnetic stimulation
Obsessive-compulsive disorder
Network meta-analysis

ABSTRACT

Background We evaluated the efficacy and safety of repetitive transcranial magnetic stimulation (rTMS) for obsessive-compulsive disorder (OCD), and ranked the relative efficacy of different stimulation protocols.

Methods We performed a search for randomised, sham-controlled trials of rTMS for OCD. The primary analysis included both a pairwise meta-analysis and a series of frequentist network meta-analyses (NMA) of OCD symptom severity. Secondary analyses were carried out on relevant clinical factors and safety.

Results 21 studies involving 662 patients were included. The pairwise meta-analysis showed that rTMS for OCD is efficacious across all protocols (Hedges' g=-0.502 [95%CI= -0.708, -0.296]). The first NMA, with stimulation protocols clustered only by anatomical location, showed that both dorsolateral prefrontal cortex (dlPFC) stimulation and medial frontal cortex stimulation were efficacious. In the second NMA, considering each unique combination of frequency and location separately, low frequency (LF) pre-supplementary motor area (preSMA) stimulation, high frequency (HF) bilateral dlPFC stimulation, and LF right dlPFC stimulation were all efficacious . LF right dlPFC was ranked highest in terms of efficacy, although the corresponding confidence intervals overlapped with the other two protocols.

Limitations Evidence base included mostly small studies, with only a few studies using similar protocols, giving a sparse network. Studies were heterogeneous, and a risk of publication bias was found.

Conclusions rTMS for OCD was efficacious compared with sham stimulation. LF right dlPFC, HF bilateral dlPFC and LF preSMA stimulation were all efficacious protocols with significant and comparable clinical improvements. Future studies should further investigate the relative merits of these three protocols.

Abbreviations: HF, high frequency; LF, low frequency; *r*, right; *l*, left; dlPFC, dorsolateral prefrontal cortex; preSMA, pre supplementary motor area; OFC, orbitofrontal cortex; mPFC, medial prefrontal cortex; ACC, anterior cingulate cortex; SMD, standardised mean difference (Hedges' g); OCD, Obsessive-compulsive disorder; rTMS, repetitive transcranial magnetic stimulation; iTBS, intermittent theta burst stimulation; cTBS, continuous theta burst stimulation; YBOCS, Yale-Brown Obsessive Compulsive Scale; CGI-S, Clinical Global Impression - Severity.

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NICE guidance

Transcranial magnetic stimulation for obsessive-compulsive disorder

Interventional procedures guidance
Published: 5 August 2020

www.nice.org.uk/guidance/ipg676

Your responsibility

This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account, and specifically any special arrangements relating to the introduction of new interventional procedures. The guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful

discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties. Providers should ensure that governance structures are in place to review, authorise and monitor the introduction of new devices and procedures.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

1 Recommendations

1.1 Evidence on the safety of transcranial magnetic stimulation for obsessive-compulsive disorder raises no major safety concerns. However, evidence on its efficacy is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research. Find out what only in research means on the NICE website.

1.2 Research should ideally be in the form of pre-registered, adequately powered, randomised controlled trials. It should report details of patient selection, including the use of concurrent therapies, type, duration and frequency of stimulation, and the intended target in the brain. Outcomes should include improvement in symptoms, quality of life and duration of effect.

2 The condition, current treatments and procedure

The condition

2.1 Obsessive-compulsive disorder is a mental health condition in which a person has obsessive thoughts (repeated, unwanted and unpleasant thoughts, images or urges). The person feels compelled to carry out compulsive (repetitive) behaviours to try to relieve the unpleasant feelings brought on by the obsessive thoughts.

Current treatments

2.2 NICE's clinical guideline on obsessive-compulsive disorder and body dysmorphic disorder describes the treatment of the disorder. Treatment options include psychological interventions and drug treatment (typically, selective serotonin reuptake inhibitors).

The procedure

2.3 Transcranial magnetic stimulation (TMS) is done with the patient awake and sitting in a comfortable chair. The operator places an electromagnetic coil over a specific region of the head. The coil delivers electromagnetic pulses through the skull that stimulate neurons (brain cells) by inducing small electrical currents within the brain. Different areas of the brain may be targeted, and a variety of stimulation protocols may be used. Treatment with TMS usually comprises daily sessions lasting about 30 minutes, for a few weeks. The aim is to reduce the symptoms of obsessive-compulsive disorder.

2.4 In repetitive TMS (rTMS), repetitive pulses of electromagnetic energy are delivered at various frequencies (low or high) or stimulus intensities. The intensity of stimulation is usually titrated against the minimum intensity needed to elicit a motor response when stimulating the motor cortex, known as the motor threshold. Determining the motor threshold for rTMS can be done visually (such as by observing targeted hand muscle movements) or by using electromyography.

2.5 Conventional rTMS is repeated individual pulses at a pre-set interval (train of pulses), and theta-burst rTMS is repeated short bursts of pulses at a pre-set interval (train of bursts). Deep TMS stimulates deeper and broader brain regions compared with conventional rTMS.

3 Committee considerations

The evidence

3.1 NICE did a rapid review of the published literature on the efficacy and safety of this procedure. This comprised a comprehensive literature search and detailed review of the evidence from 10 sources, which was discussed by the committee. The evidence included 1 systematic review and meta-analysis, 7 randomised controlled trials (1 of which is also included in the systematic review), 1 case series and 1 review of seizures reported after deep rTMS. It is presented in table 2 of the interventional procedures overview. Other relevant literature is in the appendix of the overview.

3.2 The professional experts and the committee considered the key efficacy outcomes to be reduction in obsessive-compulsive disorder symptoms and improvement in quality of life.

3.3 The professional experts and the committee considered the key safety outcomes to be headache, fatigue and concentration difficulties.

3.4 Patient commentary was sought but none was received.

Committee comments

3.5 The committee noted that there is more than 1 device available for this procedure, but that not all available devices are currently CE marked for treating obsessive-compulsive disorder.

3.6 The committee was pleased to receive commentary from a patient organisation.

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Endorsing organisation

This guidance has been endorsed by Healthcare Improvement Scotland.

Accreditation

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REVIEW

Transcranial magnetic stimulation in the treatment of adolescent depression: a systematic review and meta-analysis of aggregated and individual-patient data from uncontrolled studies

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Abstract

Transcranial magnetic stimulation (TMS) is a non-invasive treatment for adolescent major depressive disorder (MDD). Existing evidence on the efficacy of TMS in adolescent MDD awaits quantitative synthesis. A systematic literature search was conducted, and data from eligible studies were synthesized using random-effects models. Treatment-covariate interactions were examined in exploratory analyses of individual-patient data (IPD). Systematic search of the literature yielded 1264 hits, of which 10 individual studies (2 randomized trials) were included for quantitative synthesis of mainly uncontrolled studies. Individual patient data (IPD) were available from five trials (all uncontrolled studies). Quantitative synthesis of aggregated data revealed a statistically significant negative overall standardized mean change (pooled SMCC = 2.04, 95% CI [1.46; 2.61], SE = 0.29, $p < .001$), as well as a significant overall treatment response rate (Transformed Proportion = 41.30%, 95% CI [31.03; 51.57], SE = 0.05; $p < 0.001$), considering data from baseline to post-treatment. Exploratory IPD analyses suggests TMS might be more effective in younger individuals and individuals with more severe depression, and efficacy might be enhanced with certain treatment modality settings, including higher number of TMS sessions, longer treatment durations, and unilateral and not bilateral stimulation. Existing studies exhibit methodological shortcomings, including small-study effects and lack of control group, blinding, and randomization—compromising the credibility of the present results. To date, two randomized controlled trials on TMS in adolescent depression have been published, and the only large-scale randomized trial suggests TMS is not more effective than sham stimulation. Future large-scale, randomized, and sham-controlled trials are warranted. Future trials should ensure appropriate selection of patients for TMS treatment and guide precision medicine approaches for stimulation protocols.

Keywords Transcranial magnetic stimulation · Major depressive disorder · Adolescence · Meta-analysis · Individual patient data

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Clinical advances in obsessive-compulsive disorder: a position statement by the International College of Obsessive-Compulsive Spectrum Disorders

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In this position statement, developed by The International College of Obsessive-Compulsive Spectrum Disorders, a group of international experts responds to recent developments in the evidence-based management of obsessive-compulsive disorder (OCD). The article presents those selected therapeutic advances judged to be of utmost relevance to the treatment of OCD, based on new and emerging evidence from clinical and translational science. Areas covered include refinement in the methods of clinical assessment, the importance of early intervention based on new staging models and the need to provide sustained well-being involving effective relapse prevention. The relative benefits of psychological, pharmacological and somatic treatments are reviewed and novel treatment strategies for difficult to treat OCD, including neurostimulation, as well as new areas for research such as problematic internet use, novel digital interventions, immunological therapies, pharmacogenetics and novel forms of psychotherapy are discussed. ***Int Clin Psychopharmacol*** **35: 173–193 Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Keywords: evidence based, obsessive-compulsive disorder, position statement, treatments

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Introduction

Once a neglected illness, obsessive-compulsive disorder (OCD) is now recognized as a common, highly disabling and potentially treatable early-onset brain disorder.

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Section 7.0

GAP report

Hereditary Cancer Genetic Testing Guideline Update

Plain Language Summary:

Coverage question: Should OHP make major changes to the guideline on medical testing that helps determine a higher risk of developing certain types of cancer due to their family's genetic history.

Should OHP cover these tests? Yes, staff suggests adding tests recommended by a national expert group for 37 conditions, letting them simplify the guideline. In addition, strike the section about rush testing and strike the wording that requires "suitably trained" health professionals.

Coverage Question: Should major changes be made to the hereditary cancer genetic testing guideline?

Question source: Genetics Advisory Panel (GAP)

Background: The Genetics Advisory Panel (GAP) reviewed the hereditary cancer genetic testing guideline at their October 2023 meeting. This guideline was brought to GAP by staff for routine updating of the NCCN guideline references. However, members of GAP raised concerns about the guideline as current written.

1) The current guideline refers to only genetic testing for breast, ovarian, pancreatic and colon cancer syndromes. GAP members pointed out that NCCN now has guidelines for 37 different types of cancer or tumor syndromes (see the NCCN table in the packet for details). GAP recommended either adding references to all of these NCCN guidelines or removing the current section that references just the two specific NCCN guidelines.
2) There is a section in the guideline that limits testing to known BRCA variants in patients with a known family mutation. This is not current standard of care. If a patient has a known variant in one family member, there may still be other variants in the family, or other variants coming from the other parent side of the family. There is also a mention in this section about specific testing for people of Ashkenazi Jewish heritage, which has been removed from all other HERC genetic guidelines. GAP recommended striking this entire section.
3) There is a section in the guideline not allowing additional charges for rush testing. Members pointed out that there are no longer any charges for rush testing and recommended striking this section.
4) The section on genetic testing should allow providers other than the specifically mentioned types provide counseling and order testing. Breast surgeons, gynecologists, oncologic surgeons, and many others are now doing these services. GAP recommended just restricting to a health care professional with expertise in genetics to provide counseling and order testing. When

asked whether there was concern about inappropriate orders from community providers, GAP responded that this concern was much lower than concern for not allowing timely testing.

Current Prioritized List/Coverage status:

Many codes for various hereditary cancer genetic testing are on the Diagnostic Procedures File.

DIAGNOSTIC GUIDELINE D25, HEREDITARY CANCER GENETIC TESTING

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, services are provided according to the breast 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 compr Clinical Practice Guidelines in Oncology (Genetic/Familial High-Risk Assessment: Colorectal V1.2022 (6/8/22) www.nccn.org).

B) Breast and ovarian cancer syndrome genetic testing services (CPT 81162-81167, 81212, 81215-81217) for patients without a personal history of breast, ovarian and other associated cancers should be provided to high-risk 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, Ovarian and Pancreatic V1.2023 (9/7/22) www.nccn.org).

C) Breast and ovarian cancer syndrome genetic testing services (CPT 81162-81167, 81212, 81215-81217)) for women with a personal history of breast, ovarian, or other associated cancers and for men with breast or other associated cancers should be provided according to the NCCN Clinical Practice Guidelines in Oncology (Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic V1.2023 (9/7/22) www.nccn.org).

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: Ovarian and Pancreatic. V1.2023 (9/7/22) or Genetic/Familial High-Risk Assessment: Colorectal V1.2022 (6/8/22) www.nccn.org).

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.
   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.

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

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 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).

Hereditary Cancer Genetic Testing Guideline Update

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

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.

Expert guidelines:

1) NCCN
    a) See the "Summary of Genes and/or Syndromes Included/Mentioned in Other NCCN Guidelines" document in the packet
2) American Society of Clinical Oncology
    a) Only guideline is for genetic testing of advanced or metastatic cancer

HERC staff summary:

GAP had substantive revisions that they recommended to the hereditary cancer genetic testing guideline.

HERC staff recommendation:

1) Modify Diagnostic Guideline D26 as shown below
    a. First shown with new wording for ease of review
    b. Then shown with full markup for completeness

DIAGNOSTIC GUIDELINE D25, HEREDITARY CANCER GENETIC TESTING

Related to genetic testing for patients with cancers suspected to be hereditary, or patients at increased risk to due to family history, services are provided according to the Comprehensive Cancer Network Guidelines: Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic V2.2024 (9/27/23) www.nccn.org), including the table "Summary of Genes and/or Syndromes Included/Mentioned in Other NCCN Guidelines," or the Genetic/Familial High-Risk Assessment: Colorectal V1.2023 (5/30/2023) www.nccn.org).

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Hereditary Cancer Genetic Testing Guideline Update

DIAGNOSTIC GUIDELINE D25, HEREDITARY CANCER GENETIC TESTING

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~~C) Breast and ovarian cancer syndrome genetic testing services (CPT 81162-81167, 81212, 81215-81217)) for women with a personal history of breast, ovarian, or other associated cancers and for men with breast or other associated cancers should be provided according to the NCCN Clinical Practice Guidelines in Oncology (Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic V1.2023 (9/7/22) www.nccn.org).~~

~~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: Ovarian and Pancreatic. V1.2023 (9/7/22) or Genetic/Familial High-Risk Assessment: Colorectal V1.2022 (6/8/22) www.nccn.org).~~

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   ~~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.~~
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~~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 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).~~

Hereditary Cancer Genetic Testing Guideline Update

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

~~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.~~

Genetic Testing for Developmental Disabilities, Intellectual Disability, and Autism Spectrum Disorder

Plain Language Summary:

Coverage question: Should OHP update the guideline on medical testing that helps decide a higher risk of developing certain types of disabilities or disorders?

Should OHP cover these tests? Staff recommends no changes to the guideline. There are still problems with the large genetic tests for X linked disorders.

Coverage Question: Should the non-prenatal genetic testing guideline section on diagnostic evaluation for intellectual disability, developmental delay, and Autism Spectrum Disorder be updated with additional genetic tests?

Specific questions:

1) Should Phosphatase and tensin homolog (PTEN) testing be added to the autism spectrum disorder section of the non-prenatal genetic testing guideline?
2) Should large panel testing for fragile X syndrome be covered?
3) Should whole exome sequencing (WES) be added to the developmental delay section of the non-prenatal genetic testing guideline?

Question source: Holly Jo Hodges, CCO medical director; P&T staff

Background: Several questions have been raised regarding genetic testing for intellectual and developmental delay and autism spectrum disorder (ASD). Dr. Hodges had a question about adding PTEN testing. P&T requested clarification around covered tests for Rhett's syndrome due to a new medication for this condition. In investigating P&T's question, HERC staff found that large panel tests with the genes for Rett's syndrome which include fragile X testing are not included for coverage, while other fragile X testing is covered.

At the 2023 GAP meeting, HERC staff suggesting adding a section to the non-prenatal genetic testing guideline to include PTEN testing for macrocephalic boys with ASD. The other genetic tests in the AAP guideline currently have no guideline limitations and would be indicated for children with syndromic exam findings. GAP however, did not agree with the suggested guideline note changes.

Previous HSC/HERC reviews:

Coverage of X linked intellectual disability genetic panels (81470, 81471) was last discussed in 2014 as new codes. At that time, GAP recommended non-coverage. They noted that "The labs consulted on this question report a pick up rate for significant mutations is quite low, <5%."

PTEN has never been discussed as a test for autism spectrum disorder.

Genetic Testing for Developmental Disabilities, Intellectual Disability, and Autism Spectrum Disorder

Current Prioritized List/Coverage status:

Testing for Rett syndrome: CPT 81302-81304 (MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis)) are Diagnostic

CPT 81229 (Cytogenomic (genome-wide) microarray analysis) is Diagnostic

Fragile X testing: CPT 81243-81244 (FMR1 (fragile X mental syndrome) 1)) are Diagnostic. CPT 81171, 81172 (AFF2 (AF4/FMR2 family, member 2 [FMR2]) (eg, fragile X intellectual disability 2 [FRAXE]) gene analysis) are diagnostic. Testing is governed by Diagnostic Guideline D1 and D17 (prenatal and non-prenatal genetic testing guidelines).

Fragile X panel testing: CPT 81470 (X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); genomic sequence analysis panel, must include sequencing of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2) and 81471 (X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); duplication/deletion gene analysis, must include analysis of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2) are on line 662/GN173

PTEN testing: CPT 81321-81323 (PTEN (phosphatase and tensin homolog)) are Diagnostic but are limited to hereditary cancer screening by diagnostic guideline D25

DHCR7 testing: CPT 81405 (Molecular pathology procedure, Level 6) is Diagnostic

NF1 testing: CPT 81409 (Molecular pathology procedure, Level 9) and CPT 81479 (Unlisted molecular pathology procedure) are both Diagnostic

Tuberous sclerosis: (TSC1, TSC2): CPT 81406, 81405 are Diagnostic

Whole exome sequencing: CPT 81415-81416 are Diagnostic with limitations in Diagnostic Guideline D1

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

Line 662

The following Interventions are prioritized on Line 662 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
81470, 81471	X-linked intellectual disability (XLID) genomic sequence panels	Insufficient evidence of effectiveness	November, 2014

Genetic Testing for Developmental Disabilities, Intellectual Disability, and Autism Spectrum Disorder

DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE [excerpt: see Appendix A for full guideline]

A) Genetic tests are covered as diagnostic, unless they are listed below in section E1 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.

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, 81229 and 81349, Cytogenomic constitutional microarray analysis: Cover for diagnostic evaluation of individuals with intellectual disability/developmental delay; multiple congenital anomalies; or, Autism Spectrum Disorder accompanied by at least one of the following: dysmorphic features including macro or microcephaly, congenital anomalies, or intellectual disability/developmental delay in addition to those required to diagnose Autism Spectrum Disorder.
   2) CPT 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.
   3) 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.

Expert guidelines:

1) **Hyman 2020**, AAP guideline on identification, evaluation and management of children with autism spectrum disorder
   a. Recommended genetic testing
      i. Chromosomal microarray testing
      ii. Fragile X analysis
      iii. MECP2 (Rett syndrome) testing for girls
      iv. If the above do not reveal an etiology, refer to genetics and consider whole exome sequencing (WES)
   b. Other genetic testing to consider
      i. A macrocephalic boy with ASD should have PTEN testing
      ii. Syndromic appearing child: Smith-Lemi-Optiz syndrome (DHCR7)
      iii. Skin findings concerning for neurofibromatosis 1: NF1 testing

iv. Physical exam findings concerning for tuberous sclerosis: TSC1, TSC2

2) **Spector 2021**, ACMG technical standard for fragile X testing
   a. Next generation sequencing (NGS)
      i. Testing for FMR1 repeats is included in expanded carrier testing using NGS for multiple genes. Inherent limitations of short read NGS technology include difficulties sequencing across GC-rich regions, ineffective mapping of repetitive elements, and in the case of capture-based technology, PCR amplification bias of smaller alleles compared to larger full-mutation FMR1 alleles. To combat these constraints, multiple algorithms have been designed to identify clinically relevant repeat expansions from short read sequence data. However, these attempts demonstrated poor sensitivity and specificity performance in detection of FMR1 expanded alleles. Currently, short read NGS technology cannot reliably detect expanded FMR1 alleles and should not be used to rule out or confirm any FMR1-related disorders.

Other payer policies:

1) United Health Care: covers CPT 81470 and 81471 for fragile X panel testing
2) Aetna covers FMR1 gene testing but not fragile X panel testing
3) Regence BCBS: covers CPT 81470 and 81471 for fragile X panel testing

GAP input: GAP members felt that there are many syndromes that have exam findings that can indicate various genetic tests. The members felt that the staff suggested edits to Diagnostic Guideline D1 that outlined the various tests that might be indicated for persons with autism spectrum disorder or intellectual disability were not needed and might be confusing. These tests are indicated in other clinical scenarios, and putting them in Diagnostic Guideline D1 might imply that they are only covered for evaluation of patients with autism or intellectual delay. Also, "additional testing might be appropriate based on physical exam findings" is just a statement of general best practice and not needed.

GAP members felt that PTEN, testing for Rhett syndrome, etc. were all appropriate in certain clinical scenarios and it should be the intent of the HERC that such testing be allowed for patients with autism, intellectual disability or developmental delay.

<u>HERC staff proposed guideline edits NOT recommended by</u> GAP

DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE [excerpt with suggested edits only]

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:

Genetic Testing for Developmental Disabilities, Intellectual Disability, and Autism Spectrum Disorder

1) CPT 81228, 81229 and 81349, Cytogenomic constitutional microarray analysis: Cover for diagnostic evaluation of individuals with intellectual disability/developmental delay; multiple congenital anomalies; or, Autism Spectrum Disorder accompanied by at least one of the following: dysmorphic features including macro or microcephaly, congenital anomalies, or intellectual disability/developmental delay in addition to those required to diagnose Autism Spectrum Disorder.
2) CPT 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.
3) Additional testing that might be appropriate based on physical exam findings include Rett syndrome testing (CPT 81302-81304) and PTEN testing (CPT 81321-81323). Whole exome sequencing (81415-81416) may be considered when all of the testing above is non-diagnostic and after a genetic counseling/geneticist consultation.
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.

Genetic Testing for Developmental Disabilities, Intellectual Disability, and Autism Spectrum Disorder

HERC staff summary:

Panel testing for fragile X is specifically not recommended by ACMG due to the technology not being able to reliably detect expanded FMRI alleles. HERC staff recommends continued non-coverage of these panels.

HERC staff recommendation:

1) Update the date of last review for fragile X panel testing in GN173 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 662

The following Interventions are prioritized on Line 662 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**
81470, 81471	X-linked intellectual disability (XLID) genomic sequence panels	Insufficient evidence of effectiveness	~~November, 2014~~ November 2023

CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

American Academy of Pediatrics
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Identification, Evaluation, and Management of Children With Autism Spectrum Disorder

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Autism spectrum disorder (ASD) is a common neurodevelopmental disorder with reported prevalence in the United States of 1 in 59 children (approximately 1.7%). Core deficits are identified in 2 domains: social communication/interaction and restrictive, repetitive patterns of behavior. Children and youth with ASD have service needs in behavioral, educational, health, leisure, family support, and other areas. Standardized screening for ASD at 18 and 24 months of age with ongoing developmental surveillance continues to be recommended in primary care (although it may be performed in other settings), because ASD is common, can be diagnosed as young as 18 months of age, and has evidenced-based interventions that may improve function. More accurate and culturally sensitive screening approaches are needed. Primary care providers should be familiar with the diagnostic criteria for ASD, appropriate etiologic evaluation, and co-occurring medical and behavioral conditions (such as disorders of sleep and feeding, gastrointestinal tract symptoms, obesity, seizures, attention-deficit/hyperactivity disorder, anxiety, and wandering) that affect the child's function and quality of life. There is an increasing evidence base to support behavioral and other interventions to address specific skills and symptoms. Shared decision making calls for collaboration with families in evaluation and choice of interventions. This single clinical report updates the 2007 American Academy of Pediatrics clinical reports on the evaluation and treatment of ASD in one publication with an online table of contents and section view available through the American Academy of Pediatrics Gateway to help the reader identify topic areas within the report.

INTRODUCTION

Autism spectrum disorder (ASD) is a category of neurodevelopmental disorders characterized by social and communication impairment and

abstract

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Clinical reports from the American Academy of Pediatrics benefit from expertise and resources of liaisons and internal (AAP) and external reviewers. However, clinical reports from the American Academy of Pediatrics may not reflect the views of the liaisons or the organizations or government agencies that they represent.

Drs Hyman, Levy, and Myers all participated in development of the outline of material to be covered, generation of content, and editing of the document; and all authors approved the final manuscript as submitted.

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

All clinical reports from the American Academy of Pediatrics automatically expire 5 years after publication unless reaffirmed, revised, or retired at or before that time.

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Supplemental Information

SUPPLEMENTAL TABLE 14 Recurrent CNVs Most Commonly Identified in Cohorts With ASD by Using CMA Analysis

CNV Region	Frequency[a]	Common Clinical Features
16p11.2 deletion	1 in 304	ASD, DD or ID, expressive language impairment, relative or absolute macrocephaly, overweight
16p11.2 duplication	1 in 396	ASD, schizophrenia, bipolar disorder, ADHD, relative or absolute microcephaly, underweight
15q11.2-q13 (BP2–BP3) duplication	1 in 494	ASD, DD or ID, epilepsy, hypotonia, ataxia, behavior problems
15q13.2-q13.3 (BP4–BP5) deletion	1 in 659	ASD, DD or ID, epilepsy, schizophrenia, cardiac defects
1q21.1 duplication	1 in 659	ASD, DD or ID, schizophrenia, ADHD, relative macrocephaly, hypertelorism
22q11.2 duplication	1 in 659	ASD, DD or ID, hypotonia, motor delay
16p13.11 deletion	1 in 791	ASD, DD or ID, epilepsy, schizophrenia, congenital anomalies
7q11.23 duplication	1 in 989	ASD, DD or ID, growth retardation, hypotonia
16p12.2 deletion	1 in 989	ASD, DD or ID, schizophrenia, epilepsy, growth retardation, cardiac defects, microcephaly, hypotonia
17q12 deletion	1 in 1978	ASD, DD or ID, schizophrenia, renal cysts, mature-onset diabetes of the young type 5
15q13.2–13.3 (BP4–BP5) duplication	1 in 1978	ASD, DD or ID, obesity

BP2 breakpoint 2; BP3 breakpoint 3; BP4 breakpoint 4; BP5 breakpoint 5; DD developmental delay; ID intellectual disability.

[a] Moreno-De-Luca D et al[631]; the frequency of each CNV among 3955 probands with ASD from the Autism Genetic Resource Exchange, Autism Genome Project, and Simons Foundation Autism Research Initiative Simplex Collection cohorts.

SUPPLEMENTAL TABLE 13 Selected Genetic Syndromes Associated With ASD

Condition	Physical Findings	Gene	Confirmatory Testing	Importance
Fragile X syndrome	Long face, prominent forehead and jaw, large ears, joint laxity, macroorchidism after puberty in boys	*FMR1* (CGG repeat expansion, abnormal methylation)	Targeted mutation analysis (PCR and Southern blot)	Genetic counseling (X-linked dominant inheritance); all mothers of individuals with an *FMR1* full mutation are carriers of an *FMR1* premutation or full mutation; extended family counseling is necessary; premutation carriers are at risk for fragile X–associated tremor/ataxia syndrome and *FMR1*-related primary ovarian insufficiency in female patients; several targeted pharmacologic therapies are under investigation
Neurofibromatosis 1	Multiple café-au-lait macules, axillary and inguinal freckling, iris Lisch nodules, cutaneous neurofibromas	*NF1*	Clinical criteria; optimized protein truncation testing, sequence analysis, and deletion or duplication analysis are available but infrequently required	Genetic counseling (autosomal dominant inheritance); 50% de novo, 50% inherited; associated problems requiring investigation or monitoring (optic gliomas, other CNS tumors, peripheral nerve sheath tumors, vasculopathy, hypertension, orthopedic issues, osteopenia)
PTEN hamartoma tumor syndrome (includes Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome)	Marked macrocephaly, skin hamartomas, pigmented macules of the glans penis	*PTEN*	*PTEN* sequence analysis, deletion or duplication analysis	Genetic counseling (autosomal dominant inheritance with highly variable expression); associated problems requiring investigation or monitoring (significant risk of benign and malignant tumors of the thyroid, breast, and endometrium as well as intestinal polyps, colorectal cancer, renal cell carcinoma, cutaneous melanoma, and cerebellar dysplastic gangliocytoma)
Rett syndrome	Deceleration of head growth velocity, acquired microcephaly, loss of purposeful hand use, prominent hand stereotypies (especially hand wringing or clasping), apraxia, hyperventilation or breath-holding, seizures	*MECP2*	*MECP2* sequence analysis, deletion or duplication analysis	Genetic counseling (>99% de novo, <1% germline mosaicism); associated problems requiring investigation or monitoring and anticipatory guidance (failure to thrive, gastroesophageal reflux, respiratory problems, osteopenia, sudden death); targeted pharmacologic therapy under investigation
Smith-Lemli-Opitz syndrome	Characteristic facial features (narrow forehead, low-set ears, ptosis, epicanthal folds, short nose, anteverted nares), microcephaly, cleft palate, 2- to 3-toe syndactyly, postaxial polydactyly, hypospadias in male	*DHCR7*	7-dehydrocholesterol level (elevated); *DHCR7* sequence analysis available	Genetic counseling (autosomal recessive inheritance); potential role for treatment with cholesterol

SUPPLEMENTAL TABLE 13 Continued

Condition	Physical Findings	Gene	Confirmatory Testing	Importance
	patients, prenatal and postnatal growth retardation			
Timothy syndrome	Long QT interval, other ECG abnormalities (atrioventricular block, macroscopic T-wave alternans), congenital heart defects, cutaneous syndactyly, low-set ears, flat nasal bridge, thin upper lip, round facies, baldness for the first 2 y of life followed by thin scalp hair, dental abnormalities, frequent infections because of altered immune response, intermittent hypoglycemia	*CACNA1C*	Targeted mutation analysis, sequence analysis, deletion or duplication analysis	Genetic counseling, autosomal dominant, usually de novo, but parental germline mosaicism has been observed; treatment related to long QTc (β-blocker, pacemaker, implantable defibrillator) and avoidance of hypoglycemia
Tuberous sclerosis	Hypopigmented macules, angiofibromas, shagreen patches (connective tissue nevi), ungual fibromas, retinal hamartomas	*TSC1*, *TSC2*	Clinical criteria; *TSC1* and *TSC2* sequencing available	Genetic counseling (autosomal dominant inheritance); associated problems requiring investigation or monitoring (CNS tumors, seizures, renal angiomyolipomas or cysts, cardiac rhabdomyomas and arrhythmias); potential role for targeted pharmacologic therapy (mTOR inhibitors)

CACNA1C, calcium channel, voltage-dependent, L-type, α-1c subunit; CGG, cytosine-guanine-guanine; CNS, central nervous system; *DHCR7*, 7-dehydrocholesterol reductase; ECG, electrocardiogram; *FMR1*, fragile X mental retardation 1; *MECP2*, methyl CpG binding protein 2; mTOR, mammalian target of rapamycin; PCR, polymerase chain reaction; *PTEN*, phosphatase and tensin homolog; QTc, corrected QT interval; *TSC1*, tuberous sclerosis 1; *TSC2*, tuberous sclerosis 2. Adapted with permission from Myers SM, Challman TD. Autism Spectrum Disorders. In: Voigt RG, Macias MM, Myers SM, eds. *Developmental and Behavioral Pediatrics*. Elk Grove Village, IL: American Academy of Pediatrics; 2011:249–291.

SUPPLEMENTAL TABLE 15 Selected ASD Risk Genes Identified or Confirmed in Whole-Exome Studies

Gene	Gene Name	Broad Functional Categorization
SCN2A	sodium channel, voltage-gated, type II, α subunit	Synaptic functions (eg, ion channels, neurotransmitter receptors, cell adhesion molecules, microtubule assembly, scaffolding proteins, actin cytoskeleton)
GRIN2B	glutamate receptor, ionotropic, N-methyl-D-aspartate 2B	
KATNAL2	katanin p60 subunit A-like 2	
ANK2	ankyrin 2, neuronal	
DSCAM	Down syndrome cell adhesion molecule	
NRXN1	neurexin 1	
SHANK2	SH3 and multiple ankyrin repeat domains 2	
SHANK3	SH3 and multiple ankyrin repeat domains 3	
PTEN	phosphatase and tensin homolog	Intracellular signaling, activity-dependent synaptic protein synthesis and degradation
SYNGAP1	synaptic Ras GTPase activating protein 1	
DYRK1A	dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A	
POGZ	pogo transposable element with ZNF domain	
CUL3	cullin 3	
CHD2	chromodomain helicase DNA binding protein 2	Transcription regulation, chromatin remodeling
CHD8	chromodomain helicase DNA binding protein 8	
ADNP[a]	activity-dependent neuroprotector homeobox	
ARID1B	AT rich interactive domain 1B (SWI1-like)	
ASH1L	ASH1 (absent, small, or homeotic)-like	
KDM5B	lysine-specific demethylase 5B	
KMT2C	lysine-specific methyltransferase 2C	
SETD5	SET domain containing 5	
TBR1	T-box, brain, 1	

Based on de novo loss of function variants and small de novo deletions (false discovery rate < 0.01). Adapted from Sanders SJ, He X, Willsey AJ, et al; Autism Sequencing Consortium. Insights into autism spectrum disorder genomic architecture and biology from 71 risk loci. *Neuron.* 2015;87(6):1215–1233; Krumm N, O'Roak BJ, Shendure J, Eichler EE. A de novo convergence of autism genetics and molecular neuroscience. *Trends Neurosci.* 2014;37(2):95–105; Brandler WM, Sebat J. From de novo mutations to personalized therapeutic interventions in autism. *Annu Rev Med.* 2015;66:487–507; De Rubeis S, He X, Goldberg AP, et al; DDD Study; Homozygosity Mapping Collaborative for Autism; UK10K Consortium. Synaptic, transcriptional and chromatin genes disrupted in autism. *Nature.* 2014;515(7526):209–215; Bourgeron T. From the genetic architecture to synaptic plasticity in autism spectrum disorder. *Nat Rev Neurosci.* 2015;16(9):551–563; and Sanders SJ, Murtha MT, Gupta AR, et al. De novo mutations revealed by whole-exome sequencing are strongly associated with autism. *Nature.* 2012; 485(7397):237–241.

[a] Also involved in microtubule dynamics at the synapse.

SUPPLEMENTAL TABLE 16 Selected Metabolic Conditions That May (Rarely) Be Associated With an ASD Phenotype

Disorders of amino acid metabolism
Phenylketonuria (untreated)
Homocystinuria
Branched-chain ketoacid dehydrogenase kinase deficiency
Disorders of γ-aminobutyric acid metabolism
Succinic semialdehyde dehydrogenase deficiency
Disorders of cholesterol metabolism
Smith-Lemli-Opitz syndrome (7-dehydrocholesterol reductase deficiency)
Disorders associated with cerebral folate deficiency
Folate receptor 1 gene mutations
Dihydrofolate reductase deficiency
Disorders of creatine transport or metabolism
Arginine-glycine amidinotransferase deficiency
Guanidinoacetate methyltransferase deficiency
X-linked creatine transporter deficits
Disorders of carnitine biosynthesis
6-*N*-trimethyllysine dioxygenase deficiency
Disorders of purine and pyrimidine metabolism
Adenylosuccinate lyase deficiency
Adenosine deaminase deficiency
Cytosolic 5′-nucleotidase superactivity
Dihydropyrimidine dehydrogenase deficiency
Phosphoribosyl pyrophosphate synthetase superactivity
Lysosomal storage disorders
Sanfilippo syndrome (mucopolysaccharidosis type III)
Mitochondrial disorders
Mitochondrial DNA mutations
Nuclear DNA mutations
Others
Biotinidase deficiency
Urea cycle defects

Adapted from Schaefer GB, Mendelsohn NJ; Professional Practice and Guidelines Committee. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. *Genet Med.* 2013;15(5):399–407; Legido A, Jethva R, Goldenthal MJ. Mitochondrial dysfunction in autism. *Semin Pediatr Neurol.* 2013;20(3):163–175; Jiang YH, Wang Y, Xiu X, Choy KW, Pursley AN, Cheung SW. Genetic diagnosis of autism spectrum disorders: the opportunity and challenge in the genomics era. *Crit Rev Clin Lab Sci.* 2014;51(5):249–262; and Frye RE. Metabolic and mitochondrial disorders associated with epilepsy in children with autism spectrum disorder. *Epilepsy Behav.* 2015;47:147–157.

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alleles. The term *subpopulation* of an allele is recommended. See Table 3 for example interpretation paragraphs for use in reporting.

FX 3.3.1.4: All positive results should state that genetic counseling is recommended, and testing is available for at-risk family members.

FX 3.3.2: The following descriptive elements may appear, with caution:

FX 3.3.2.1: The size of the alleles may be reported and could be of clinical use for individuals who are heterozygous for the premutation. The premutation allele size may be used for risk assessment in determining the chance of expansion in the offspring of these individuals and in determining the chance of FXTAS or FXPOI. If so, the precision used in quoting the size must be supportable by the precision of the size marker used, the sharpness of the bands or peaks, degree of stutter, and so on. It may be appropriate to state a range or use qualifying terms such as "approximately." Descriptions such as "positive for an allele with 55–200 repeats" are ambiguous and should not be included on the laboratory report.

The CAP/ACMG Biochemical and Molecular Genetics Resource Committee published results of laboratory performance on the CAP proficiency surveys for molecular genetic testing for fragile X conducted between 2001 and 2009[73] and the acceptable range for sizing CGG repeats for fragile X is based on these results. Acknowledging the technical limitations of size analysis, the ACMG supports the following grading criteria for the CAP/ACMG proficiency testing survey: consensus size ±5 repeats for alleles with <55 repeats, consensus size ±10 repeats for alleles with 56–100 repeats, and consensus size ±2 SDs for alleles with >100 repeats.

FX 3.3.2.2: Description of methylation may be provided. The two kinds of methylation must be clearly distinguished: methylation due to X-inactivation and hypermethylation of full mutations. The term *methylation mosaic* or *incomplete methylation* may be used if not all molecules in a full mutation are hypermethylated.

FX 3.3.2.3: Occasionally unexpected patterns are seen that may not fit within the descriptions provided here. In those cases, a detailed description may be helpful. For example, methylation PCR may exhibit a pattern of size and methylation mosaicism with subpopulations of premutations (<200 CGG repeats), which are methylated, and full mutations (>200 CGG repeats), which are unmethylated.

FX 3.3.3: Helpful points on alternative diagnoses may be included

FX 3.3.3.1: There are rare forms of FMRP deficiency not caused by CGG expansion, which may not be detected by this test.

FX 3.3.3.2: Intellectual disability associated with other fragile X sites, FRAXE, or other gene variants will not be detected with this test.

FX 3.3.3.3: DNA analysis for FXS should be performed as part of a comprehensive genetic evaluation that includes chromosomal microarray and a five-cell screen for chromosome rearrangement analysis as recommended by ACMG.[116,117]

FX 3.3.4: Comments on phenotype, if included, should be abstract rather than case specific. The following concepts apply:

FX 3.3.4.1: All males with full mutations have FXS to some degree. The severity cannot be predicted from the size of the full mutation, but if premutations are also present or if the majority of the full-mutation molecules are unmethylated, the phenotype may be less severe.

FX 3.3.4.2: Females with full mutations exhibit a wide spectrum of phenotypes. They may be as severely affected as a male with an expanded fragile X allele (which is itself a range of phenotypes). Females with full mutations may also exhibit very mild learning disabilities or have no detectable deficits. The severity cannot be predicted from the size of the full mutation, nor can it be predicted from the pattern of X-inactivation in blood.

FX 3.3.4.3: Individuals with heterozygous premutations should not be interpreted as unaffected. Females who carry a premutation are at risk for FXPOI and FXTAS. Males with the premutation are at risk for FXTAS. Both sexes are at risk for FXAND. If an individual referred for diagnostic testing due to intellectual disability, autism, or learning disability is found to carry a premutation, the upper end of the premutation is often associated with these problems, because FMRP levels are lower than normal above 120 repeats. FMRP deficiency or mosaicism for a full mutation can be detected.

FX 3.3.4.4: Individuals with intermediate alleles should be interpreted as unaffected. Even more so than a premutation, an intermediate allele is considered a coincidence when found in an individual referred for diagnostic testing due to intellectual disability, learning disability, or autism. FMRP deficiency or mosaicism for a full mutation can be investigated by methylation-sensitive Southern blot analysis but with less likelihood of success because intermediate alleles are common in the general population.

FX 3.3.5: Comments on reproductive risk, if included, should be abstract rather than case specific. The following concepts apply:

FX 3.3.5.1: All affected males and most affected females inherit their variant from their mothers. Mothers carry either a premutation or full-mutation allele. Females with heterozygous premutations may have inherited their *FMR1* allele from either their mother or father.

FX 3.3.5.2: Women with full mutations have a theoretical 50% chance of passing on the full mutation with each pregnancy.

FX 3.3.5.3: Women with premutations have a 50% chance of passing on the fragile X variant with each pregnancy. If it is passed on, the chance the allele will increase to a full mutation depends on its size in the mother and the number of AGG interruptions. Probabilities range from 3% for maternal alleles with CGG repeats from 55 to 59 (1/23 transmissions) to ~100% for maternal alleles with 90 CGGs and above.[75] The smallest allele known to expand to the full mutation is 56 repeats.[64] Laboratories should be familiar with publications on this topic,[75,81,82,102,118] including any current publications.

FX 3.3.5.4: Men with premutations will almost always pass premutation alleles to all their daughters. An extremely rare phenomenon involves males with premutations who have had daughters with full mutations, apparently due to gonadal mosaicism for full mutations.[119–121] The sons of men with the premutation are not at risk for developing the FXS or FXTAS since they inherit their father's Y chromosome.

FX 3.3.5.5: To date, there have been no reports of males or females with heterozygous intermediate alleles having offspring with an *FMR1* allele in the full-mutation range. Instability may be identified if the allele can be traced through the family to a known full mutation or unambiguous premutation. In the absence of such a connection, it may be possible to show meiotic instability or a specific repeat sequence pattern (absence of AGG interruptions) that is at higher risk for instability. Testing for AGG status is available in a limited number of laboratories.

FX 4: ALTERNATIVE TESTING METHODS

FX 4.1: Next-generation sequencing (NGS)

Testing for *FMR1* repeats is included in expanded carrier testing using NGS for multiple genes. Inherent limitations of short read NGS technology include difficulties sequencing across GC-rich regions, ineffective mapping of repetitive elements, and in the case of capture-based technology, PCR amplification bias of smaller alleles compared to larger full-mutation *FMR1* alleles.

To combat these constraints, multiple algorithms have been designed to identify clinically relevant repeat expansions from short read sequence data. However, these attempts demonstrated poor sensitivity and specificity performance in detection of *FMR1* expanded alleles.[122,123] Currently, short read NGS technology cannot reliably detect expanded *FMR1* alleles and should not be used to rule out or confirm any *FMR1*-related disorders. Advances in genome testing, using PCR-free methods, reduces some of the difficulties in sequencing through repetitive regions. Combined with new analysis software, repeat disorders may be identified from PCR-free genomes,[124–126] although genome sequencing for fragile X is cost prohibitive for expanded carrier testing. In those applications, *FMR1* testing is often performed separately.

Single-molecule, real-time (SMRT) long-read sequencing is able to sequence through a full-mutation allele of 750 CGG repeats (~2 kb) and may be used to distinguish the number and location of AGG interruptions.[94,127] Long-read technology is not yet widely available for clinical use, though this may change as error rate and costs decrease, and more bioinformatics tools become available for clinical application. Currently, TP-PCR and Southern blot methods remain the gold standards for identification of expanded *FMR1* alleles and CGG repeat quantification.

FX 4.2: Cytogenetic evaluation

Testing for the fragile site FRAXA at Xq27 is no longer an acceptable diagnostic method. Clinical and analytical specificity and sensitivity are both insufficient.

FX 4.3: Protein analysis

Immunohistochemical staining for FMRP is a valid diagnostic method in lymphocytes.[71] Willemsen et al. demonstrated that staining for the FMRP protein in chorionic villus samples could be used as an alternative prenatal diagnostic method for detection of full mutations in male fetuses.[69] The situation is more complicated in female fetuses for which some chorionic villi may be completely positive and others from the same sample may be completely negative for FMRP staining. The authors' data shed light on the timing of X-inactivation in chorionic villus cells of the female fetus. The diagnostic application of this method is not recommended at this time for the prenatal diagnosis of females carrying *FMR1* full mutations.

FX 5: POLICY STATEMENTS

FX 5.1

The American College of Medical Genetics and Genomics issued a policy statement titled Fragile X Syndrome: Diagnosis and Carrier Testing in 1994,[128] which was updated in October 2005.[63] This document is also available online (http://www.acmg.net). These Standards are in general agreement with that statement.

FX 5.2

The NSGC also published practice guidelines to assist genetic counselors in providing accurate risk assessment and appropriate educational and supportive counseling for individuals with positive test results and families affected by *FMR1*-associated disorders.[64] Additionally, in 2017, ACOG issued a Committee Opinion, No. 691, on carrier screening for genetic conditions, including fragile X syndrome.[60] The Standards presented here are in general agreement with those opinions.

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2024 CPT Code Review: Tumor Testing

Issue:

Among the 2024 CPT codes are 6 new codes for next generation sequencing (NGS) of tumor tissue. The HERC discussed NGS at their September 2023 meeting and adopted a new diagnostic guideline to apply to all NGS testing of malignant tissue.

Multiple CPT codes for "targeted genomic sequence analysis panel" (for example, CPT 81450-81456) are on the Diagnostic Procedures File. FoundationOne CDx (CPT 0037U) was added to the Diagnostic Procedures file at the September 2023 meeting.

One additional PLA (proprietary analysis code) was added in the 2024 code cycle for Quest Labs NGS lab. Dr. Carl Stevens (formerly of CareOregon) recommended coverage for this code as it is a commonly used test by local oncologists.

On further review of new PLA codes, several other new codes were found for NGS testing of cancer tissue. These codes are also proposed for coverage, governed by the new NGS guideline.

New codes:

CPT code	Code description
81457	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, microsatellite instability
81458	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, copy number variants and microsatellite instability
81459	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements
81462	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants and rearrangements
81463	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis, copy number variants, and microsatellite instability
81464	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and re

PLA code	Code description	Test name
0379U	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA (523 genes) and RNA (55 genes) by nextgeneration sequencing, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability, and tumor mutational burden	Solid Tumor Expanded Panel, Quest Diagnostics®
0388U	Oncology (non-small cell lung cancer), next-generation sequencing with identification of single nucleotide variants,	InVisionFirst®-Lung Liquid Biopsy

	copy number variants, insertions and deletions, and structural variants in 37 cancer-related genes, plasma, with report for alteration detection	
0391U	Oncology (solid tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded (FFPE) tissue, 437 genes, interpretive report for single nucleotide variants, splice-site variants, insertions/deletions, copy number alterations	Strata SelectTM
0409U	Oncology (solid tumor), DNA (80 genes) and RNA (36 genes), by next-generation sequencing from plasma, including single nucleotide variants, insertions/deletions, copy number alterations, microsatellite instability, and fusions, report showing identified mutations with clinical actionability	LiquidHALLMARK®
0413U	Oncology (hematolymphoid neoplasm), optical genome mapping for copy number alterations, aneuploidy, and balanced/complex structural rearrangements, DNA from blood or bone marrow, report of clinically significant alterations	DH Optical Genome Mapping/Digital Karyotyping Assay

New guideline adopted September 2023, effective 1/1/2024

DIAGNOSTIC GUIDELINE DX, NEXT GENERATION SEQUENCING OF MALIGNANCIES

Next Generation Sequencing (NGS, for example CPT 81479, 81455, 0037U) is covered when all of the following requirements are met:

1) The patient has
    a. Either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; AND
    b. Has not been previously tested using the same NGS test for the same primary diagnosis of cancer, unless the criteria in 4) below are met; AND
    c. Decided to seek further cancer treatment (for example, therapeutic chemotherapy) and has adequate performance status (ECOG 0-2) to undergo such treatment; AND
2) The diagnostic laboratory test using NGS must have:
    a. Clinical Laboratory Improvement Amendments (CLIA)-certification; AND
    b. The test is being used as a companion diagnostic test in accordance with Food & Drug Administration (FDA)-approved therapeutic labeling; AND
    c. Results provided to the treating physician for management of the patient using a report template to specify treatment options; AND
3) A single CPT or HCPCS code is covered for each multigene panel performed on tumor tissue. Additional codes for individual genes and for molecular pathology procedures CPT 81400-81408 are excluded from coverage when the multigene panel is covered under the appropriate CPT or HCPCS code.
4) Repeat NGS testing may be required in the setting of patients who have clinically progressed per standardized professional guidelines after therapy. Coverage in this situation is limited to 3 times per primary malignancy unless there is indication for additional testing after individualized review of medical necessity.

2024 CPT Code Review: Tumor Testing

GAP input:

Carl Stevens raised concerns about section 1A of the new next generation sequencing guidelines. Currently, section 1A limited NGS testing to "Either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer." This was written to be consistent with current CMS guideline wording. However, Dr. Stevens notes that there are many cases in which testing early in the course of a cancer diagnosis is preferable. Some types of cancer have targeted therapies if they contain specific gene mutations. Some types of cancer with specific mutations can be cured with targeted therapy in early stages. Dr. Stevens felt that any cancer that has a molecular profile that is amenable to any of the targeted therapy should be allowed to have targeted therapy rather than general chemotherapy. He suggested changing 1A to "tissue diagnosis confirming cancer and have been evaluated by an oncologist or oncologic surgeon."

2024 CPT Code Review: Tumor Testing

HERC staff recommendations:

1) Place the following CPT codes on the Diagnostic Procedures File subject to the new NGS guideline
    a. 81547 Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, microsatellite instability
    b. 81548 Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, copy number variants and microsatellite instability
    c. 81549 Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements
    d. 81462 Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants and rearrangements
    e. 81463 Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis, copy number variants, and microsatellite instability
    f. 81464 Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and re
2) Place 0the following PLA codes on the Diagnostic Procedures File
    a. 0379U Solid Tumor Expanded Panel, Quest Diagnostics®
    b. 0388U InVisionFirst®-Lung Liquid Biopsy
    c. 0391U Strata SelectTM
    d. 0409U LiquidHALLMARK®
    e. 0413U DH Optical Genome Mapping/Digital Karyotyping Assay
3) Modify the new guideline regarding next generation sequencing of malignancies as shown below

DIAGNOSTIC GUIDELINE DX, NEXT GENERATION SEQUENCING OF MALIGNANCIES

Next Generation Sequencing (NGS, for example CPT 81479, 81455, 0037U) is covered when all of the following requirements are met:

1) The patient has
    a. ~~Either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer~~ ~~a~~ tissue diagnosis confirming cancer and has been evaluated by an oncologist or oncologic surgeon; AND
    b. Has not been previously tested using the same NGS test for the same primary diagnosis of cancer, unless the criteria in 4) below are met; AND
    c. Decided to seek further cancer treatment (for example, therapeutic chemotherapy) and has adequate performance status (ECOG 0-2) to undergo such treatment; AND
2) The diagnostic laboratory test using NGS must have:
    a. Clinical Laboratory Improvement Amendments (CLIA)-certification; AND
    b. The test is being used as a companion diagnostic test in accordance with Food & Drug Administration (FDA)-approved therapeutic labeling; AND
    c. Results provided to the treating physician for management of the patient using a report template to specify treatment options; AND
3) A single CPT or HCPCS code is covered for each multigene panel performed on tumor tissue. Additional codes for individual genes and for molecular pathology procedures CPT 81400-81408

are excluded from coverage when the multigene panel is covered under the appropriate CPT or HCPCS code.

4) Repeat NGS testing may be required in the setting of patients who have clinically progressed per standardized professional guidelines after therapy. Coverage in this situation is limited to 3 times per primary malignancy unless there is indication for additional testing after individualized review of medical necessity.

GAP ACMG Guideline Reference Update

Issue: The American College of Medical Genetics (ACMG) recently updated their recommendations for cystic fibrosis (CF) carrier screening. Previously they recommended a 23 gene panel. They have revised their recommendation to include 100 mutations/gene variants, due to advances in genetics and gene identification (see Deignan 2023). On review of this issue, GAP members raised concerns that the current testing criteria for children who are symptomatic is a tiered testing strategy, while carrier screening for CF allows all tests with no tier [from guideline below: Screening for cystic fibrosis carrier status (CPT 81220-81224)]. The Deignan paper supports sequencing including deletions and duplications, which is more consistent with the current carrier screening. GAP recommends simplifying the diagnostic testing criteria to mirror the carrier screening criteria.

On review of this issue, HERC staff noted that there are two ACMG references to two separate guidelines in Diagnostic Guideline D1 that are not clearly identified.

HERC staff recommendation:

1) Update Guideline Note 3 as shown below
    a. Update the CF carrier screening reference to the current ACMG standard
    b. Update the guideline to clearly delineate the two ACMG guidelines referenced
        i. The expanded carrier screening guideline is now #1 and the CF guideline is #2

DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE

A) Genetic tests are covered as diagnostic, unless they are listed below in section E1 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 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, 81229 and 81349, Cytogenomic constitutional microarray analysis: Cover for diagnostic evaluation of individuals with intellectual disability/developmental delay; multiple congenital anomalies; or, Autism Spectrum Disorder accompanied by at least one of the following: dysmorphic features including macro or microcephaly, congenital anomalies, or intellectual disability/developmental delay in addition to those required to diagnose Autism Spectrum Disorder.
2) CPT 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.
3) 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 preconception testing/carrier screening:

1) The following tests are covered for a pregnant patient or patient contemplating pregnancy as well as the male reproductive partner:

a) Screening for genetic carrier status with the minimum testing recommended by the American College of Obstetrics and Gynecology:
   i) Screening for cystic fibrosis carrier status (CPT 81220-81224)
   ii) Screening for fragile X status (CPT 81243, 81244, 81171, 81172)
   iii) Screening for spinal muscular atrophy (CPT 81329)
   iv) Screening 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.
   v) Screening for hemoglobinopathies (CPT 83020, 83021)
b) Expanded carrier screening (CPT 81443): A genetic counseling/geneticist consultation must be offered prior to ordering test and after test results are reported. Expanded carrier testing is ONLY covered when all of the following are met:
   i) the panel includes only genes with a carrier frequency of ≥ 1 in 200 or greater per ACMG Guideline (2021)[1],
   ii) the included genes have well-defined phenotype, AND
   iii) the included genes result in conditions have a detrimental effect on quality of life OR cause cognitive or physical impairment OR require surgical or medical intervention, AND
   iv) the included genes result in conditions have an onset early in life, AND
   v) the included genes result in conditions that must be diagnosable prenatally to inform antenatal interventions and/or changes in delivery management and/or education of parents about special needs after birth.

F) 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 ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS.

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~~, 81221, 81222, 81223~~ 81224: 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* [2] ~~(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) CPT 81224, CFTR (cystic fibrosis transmembrane conductance regulator) (e.g. cystic fibrosis) gene analysis; introm 8 poly-T analysis (e.g. male infertility): Covered only after genetic counseling.
   d) CPT 81225-81227, 81230-81231, 81418, 0380U (cytochrome P450). Covered only for determining eligibility for medication therapy if required or recommended in the FDA labelling for that medication. These tests have unproven clinical utility for decisions regarding medications when not required in the FDA labeling (e.g. psychiatric, anticoagulant, opioids).
   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.
   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 81332, SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z): The alpha-1-antitrypsin protein level should be the first line test for a suspected diagnosis of AAT deficiency in symptomatic individuals with unexplained liver disease or obstructive lung disease that is not asthma or in a middle age individual with unexplained dyspnea. Genetic testing of the anpha-1 phenotype test is appropriate if the protein test is abnormal or borderline. The genetic test is appropriate for siblings of people with AAT deficiency regardless of the AAT protein test results.

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

m) CPT 81430-81431, Hearing loss (e.g., 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.

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

o) CPT 81425-81427, whole genome sequencing: testing is only covered when
i) The testing is for a critically ill infant up to one year of age admitted to an inpatient intensive care unit (NICU/PICU) with a complex illness of unknown etiology; AND
ii) Whole genome sequencing is recommended by a medical geneticist or other physician sub-specialist, including but not limited to a neonatologist or pediatric intensivist with expertise in the conditions and/or genetic disorder for which testing is being considered.

~~* American College of Medical Genetics Standards and Guidelines for Clinical Genetics Laboratories. 2008 Edition, Revised 7/2018 and found at http://www.acmg.net/PDFLibrary/Cystic-Fibrosis-Population-Based-Carrier-Screening-Standards.pdf.~~

[1] Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG) 2021, found at https://www.gimjournal.org/action/showPdf?pii=S1098-3600%2821%2905152-2

[2] American College of Medical Genetics Statement: updated recommendations for CFTR carrier screening 2023, found at https://www.gimjournal.org/action/showPdf?pii=S1098-3600%2823%2900880-8

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Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG)

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*The Board of Directors of the American College of Medical Genetics and Genomics approved this practice resource on 12 April 2021.

COMPETING INTERESTS

M.A., N.T.L., M.T.B. and E.C. are directors of molecular testing laboratories that offer carrier screening. J.S.D. is a member of the Advisory Board for Informed DNA and Medical Co-Director at Insight Medical Genetics in Chicago, which provides genetic laboratory services. The other authors declare no competing interests.

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Disclaimer: This practice resource is designed primarily as an educational resource for medical geneticists and other clinicians to help them provide quality medical services. Adherence to this practice resource is completely voluntary and does not necessarily assure a successful medical outcome. This practice resource should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. In determining the propriety of any specific procedure or test, the clinician should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen.

Clinicians are encouraged to document the reasons for the use of a particular procedure or test, whether or not it is in conformance with this practice resource. Clinicians also are advised to take notice of the date this practice resource was adopted, and to consider other medical and scientific information that becomes available after that date. It also would be prudent to consider whether intellectual property interests may restrict the performance of certain tests and other procedures.

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Abstract

Carrier screening began 50 years ago with screening for conditions that have a high prevalence in defined racial/ethnic groups (e.g., Tay–Sachs disease in the Ashkenazi Jewish population; sickle cell disease in Black individuals). Cystic fibrosis was the first medical condition for which panethnic screening was recommended, followed by spinal muscular atrophy. Next-generation sequencing allows low cost and high throughput identification of sequence variants across many genes simultaneously. Since the phrase “expanded carrier screening” is nonspecific, there is a need to define carrier screening processes in a way that will allow equitable opportunity for patients to learn their reproductive risks using next-generation sequencing technology. An improved understanding of this risk allows patients to make informed reproductive decisions. Reproductive decision making is the established metric for clinical utility of population-based carrier screening. Furthermore, standardization of the screening approach will facilitate testing consistency. This practice resource reviews the current status of carrier screening, provides answers to some of the emerging questions, and recommends a consistent and equitable approach for offering carrier screening to all individuals during pregnancy or preconception.

INTRODUCTION

Carrier screening is used to identify individuals or couples that are at risk to have a child with an autosomal recessive or X-linked genetic disorder. Throughout this document, the term “carrier” specifically refers to individuals who are heterozygous for a pathogenic or likely pathogenic variant in an autosomal recessive or X-linked condition. Once identified, carriers of these disorders can become educated about their risks and consider a range of reproductive options. Historically, criteria for screening have included: phenotype severity that may impact decision making,[1,2] high prevalence of carriers in the screened population,[2] established analytic validity of screening methods,[2,3] predictable genotype–phenotype correlation,[2] available prenatal diagnosis and reproductive options.[2,4] Although general principles remain similar today these do not speak to the genes that should be included as part of routine carrier screening.

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ACMG STATEMENT

Updated recommendations for *CFTR* carrier screening: A position statement of the American College of Medical Genetics and Genomics (ACMG)

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Introduction

Pathogenic variants in the *CFTR* gene are causative of cystic fibrosis (CF) as well as CF-related disorders, such as isolated congenital bilateral absence of the vas deferens (CBAVD). In 2001, several professional organizations joined in acknowledging the importance and technologic advances that would make CF amenable to population-based carrier screening.[1] However, the technology and knowledge had not advanced far enough to allow for an equitable application. Variant databases were far less advanced when compared with those that are easily and widely accessible today. Sequencing technology was also early in development. This limited screening to small sets of variants that were most commonly characterized in Ashkenazi Jewish and Northern European populations using targeted, allele-specific testing approaches rather than DNA sequencing. For this reason, recommendations at that time were that screening should be "offered" to those of

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Section 8.0

New Discussion Items

Computer Assisted Bronchoscopy 2023 Review

Plain Language Summary:

Coverage question: Should OHP cover a procedure that uses computer pictures to help guide where a doctor looks in the lungs to get sample tissue?

Should OHP cover this treatment? Yes, newly published medical studies show this procedure is both safe and accurate.

Coverage Question: Should computer assisted bronchoscopy be moved from Line 662/GN173 and made diagnostic?

Question source: Dr. Shalini Mehta and Dr. Brian Delmonaco, pulmonologists in Corvallis OR

Background: Computer assisted bronchoscopy, also known as electromagnetic navigation bronchoscopy (ENB) or navigational bronchoscopy, is a procedure for diagnosing peripheral lung lesions. When ENB is used for diagnostic purposes, CT scans are first collected and downloaded into the system's software, which reconstructs the scans into three- dimensional images of the lungs. The individual is sedated and positioned over an electromagnetic location board and bronchoscopy is initiated. A microsensor probe is inserted through the working channel of the bronchoscope into the airways. The sensor automatically registers the points and maps the appropriate route to peripheral lung lesions using the combined CT images and computer software. To navigate, the physician views the computer monitor and advances the guide to reach suspicious peripheral lung lesions. Tools can be inserted through the working channel to the lesion to collect samples.

Electromagnetic navigation (EN) guided bronchoscopy is used to assist in biopsy of small peripheral lung lesions to determine if they are non-small cell lung cancer. Several other modalities exist to assist in diagnosing such lesions, including endobronchial ultrasound (EBUS) bronchoscopy (CPT 31652-31654, Diagnostic) and transthoracic needle biopsy.

From Dr. Mehta:

> Our societies (AABIP, ATS, and CHEST) include physicians providing care for patients with peripheral lung lesions (PLLs) who are working to improve the provision of lung cancer care in a timely and cost-effective manner. The established published evidence and recognized clinical practice guidelines support our request and recommendation to archive the associated policy and remove the 'investigation and not medically necessary' status for Navigational Bronchoscopy. Herein, we present the evidence base that supports our position.
>
> The current policy points out that most PLLs are diagnosed using the transthoracic needle aspiration (TTNA) technique because it has a higher diagnostic yield than standard

bronchoscopy or electromagnetic navigation bronchoscopy (ENB) and is safe in most patients with PLLs. Meta-analyses of TTNA biopsies published within the radiology literature show complication rates that are several times higher than those seen with ENB (Eur Radiol. 2017 Jan;27(1):138-148; J Thorac Oncol. 2022 Apr;17(4):519-531). Numerous target lesion factors may reduce the diagnostic yield of TTNA and are contraindications for TTNA: the presence of emphysema or blebs, location near major vessels, uncontrollable cough, and a site requiring a significant amount of lung to be traversed or which is near the diaphragm. TTNA may be inappropriate and higher risk for many patients in these cases. Recent cost-effectiveness studies of diagnosis and staging for lung cancer show that CT-guided biopsy alone, when compared with the most cost-effective bronchoscopic strategy, results in more complications, requires more time to complete the evaluation, has a higher rate of undetected mediastinal lymph node involvement (N2-3 disease), and an increased risk of mortality (Chest. 2021; 160(6):2304-2323). Furthermore, deviation from guidelines and performance of a CT-guided biopsy first results in a 17% higher rate of pneumothorax and increases cost by $1,000 per patient.

Several meta-analyses have evaluated the risk of pleural recurrence after a TTNA compared to alternatives (surgery and bronchoscopic biopsy). A recent study (Thorax. 2021 Jun;76(6):582-590) analyzed 2394 patients (TTNA, 1158 patients versus other [bronchoscopy, surgery], 1236 patients) with a median follow-up after surgery of 60.7 months. Compared with other diagnostic procedures, TTNA was associated with a higher risk for ipsilateral pleural recurrence, which manifested solely and concomitantly with other metastases. Furthermore, reductions in the time to recurrence, lung cancer-specific survival, and overall survival were observed in patients <55 years who underwent TTNA. Recently published data also suggests that even patients with small peripheral lesions suspected of lung cancer (T1 tumors) benefit from staging due to the high rate of mediastinal disease (Chest. 2020;158(5):2192-2199). Therefore, committing these patients to a CT-guided biopsy first not only puts them at higher risk for complications, but it will also lead to repeat interventions such as subsequent bronchoscopy for staging, and thus, delay the time to treatment and risk tumor upstaging.

Non-coverage of navigational bronchoscopy leaves our patients without an option for minimally invasive sampling to achieve a tissue diagnosis and staging, as indicated. Regarding navigational bronchoscopy and the coverage of procedures for the evaluation of pulmonary nodules, over 95% of health plans have chosen to extend coverage to navigational bronchoscopy, either by archiving and inactivating a non-coverage policy or by issuing a favorable coverage policy:

- The evidence for sensitivity and the complication rates of navigational bronchoscopy are adequately described in the literature. Navigational bronchoscopy is a component of the Standard of Care in evaluating patients with PLLs.
- They recognize that the trade-offs of specific risks and benefits in the evaluation of individual patients is best done in the context of informed consent between clinicians and patients, based on current guidelines and published evidence.

The clinical guidelines and recommendations published by the American College of Chest Physicians (CHEST), American Thoracic Society (ATS), National Comprehensive Cancer Network (NCCN), UpToDate, and Blue Cross Blue Shield Association (BCBSA) confirm the widely accepted evidence-based guideline that navigational bronchoscopy is a standard of care procedure for patients with peripheral lung lesions.

NCCN Non-Small Cell Lung Cancer (NSCLC) 2022 guidelines:

Computer Assisted Bronchoscopy 2023 Review

"The preferred biopsy technique depends on the disease site and is described in the NSCLC algorithm. For example, radial endobronchial ultrasound (EBUS), navigational bronchoscopy, or transthoracic needle aspiration (TTNA) are recommended for patients with suspected peripheral nodules."

British Thoracic Society guidelines for the investigation and management of pulmonary nodules recommend augmenting the yield from bronchoscopy using either radial endobronchial ultrasound, fluoroscopy, or electromagnetic navigation (ENB) (Thorax. 2015;70:ii1–ii54)

We trust that the information we have outlined and support from our colleagues and other professional societies show that Navigation Bronchoscopy has the evidence base to support its coverage in appropriately selected patients. It is a Standard of Care approach in evaluating patients with PLLs.

Previous HSC/HERC reviews:

Computer assisted bronchoscopy was first reviewed in December, 2009 as part of the 2010 CPT code review. At that time, very little literature was found on the topic and it was determined to be experimental.

Computer assisted bronchoscopy was last reviewed in 2021. The 2021 review included a 2019 NICE technology review and the NCCN 2021 guideline for non-small cell lung cancer. The summary of the 2021 review stated "Computer assisted bronchoscopy is one option for biopsy of a peripheral lung lesion. NICE found the literature to be questionable, and recommended consideration of the technology only for patients who could not undergo transthoracic biopsy. NCCN lists "navigational bronchoscopy" as just one option for evaluating peripheral lung nodules. Private payers consider this technology to be experimental and are not currently covering it. Multiple other diagnostic tests for peripheral lung lesions, such as endobronchial ultrasound (EBUS) bronchoscopy and transthoracic needle biopsy, are currently covered."

Current Prioritized List/Coverage status:

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

Line 662

The following Interventions are prioritized on Line 662 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
31627	Computer assisted bronchoscopy	Insufficient evidence of effectiveness	March 2021

On the Diagnostic Procedures File:

Computer Assisted Bronchoscopy 2023 Review

CPT 31623 Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with brushing or protected brushings
CPT 31624 with bronchial alveolar lavage
CPT 31625 with bronchial or endobronchial biopsy(s), single or multiple sites
CPT 31628 with transbronchial lung biopsy(s), single lobe
CPT 31629 with transbronchial needle aspiration biopsy(s), trachea, main stem and/or lobar bronchus(i)
CPT 31632 with transbronchial lung biopsy(s), each additional lobe
CPT 31633 with transbronchial needle aspiration biopsy(s), each additional lobe
CPT 31652-31654 Endobronchial ultrasound (EBUS)
CPT 32408 Transthoracic needle aspiration (TTNA)

Evidence:

1) **Jiang 2020**, meta analysis of navigation bronchoscopy of peripheral pulmonary lesions (PPL)
    a. N=10 studies (2131 patients)
        i. Studies comparing diagnostic yield of navigation bronchoscopy for peripheral pulmonary lesions (PPL) compared to non-navigation bronchoscopy
            1. Comparison methods: endobronchial ultrasound (EBUS), Xray
        ii. 5 RCTs, 2 non randomized trials, 3 case=control studies
    b. Diagnostic yield of navigation bronchoscopy was statistically higher than non-navigation bronchoscopy for PPLs (odds ratio [OR] 1.69, 95% confidence interval [CI] 1.32, 2.18, P < 0.001), particularly for PPLs in the peripheral third lung (OR 2.26, 95% CI 1.48, 3.44, P < 0.001) and for bronchus sign positive PPLs (OR 2.26, 95% CI 1.21, 4.26, P = 0.011). Navigation bronchoscopy had better performance than non-navigation bronchoscopy when PPLs were ≤ 20 mm (OR 2.09, 95% CI 1.44, 3.03, P < 0.001). It also elevated diagnostic yield of malignant PPLs (OR 1.67, 95% CI 1.26, 2.22, P < 0.001) and PPLs in the bilateral upper lobes (OR 1.50, 95% CI 1.09, 2.08, P = 0.014)
    c. A total of seven studies included in the analysis reported complications. Prevalence of complications reported in navigation bronchoscopy and non-navigation bronchoscopy was 3.22% and 2.67%, respectively. There was no significant difference between onset of complications of the above two groups (OR 1.28, 95% CI 0.73, 2.25, P = 0.397). Pneumothorax and hemorrhage were the most common complications reported
    d. Conclusions: Navigation bronchoscopy enhanced diagnostic yield when compared to non-navigation bronchoscopy, particularly for PPLs in the peripheral third lung, PPLs being bronchus sign positive, PPLs ≤ 20 mm, malignant PPLs and PPLs in the bilateral upper lobes.
2) **McGuire 2020**, systematic review and meta-analysis of the accuracy and sensitivity of radial-endobronchial ultrasound and electromagnetic navigation bronchoscopy for sampling of peripheral pulmonary lesions
    a. N=41 studies (2988 lung nodules) in 3204 patients
        i. N=2101 radial-endobronchial ultrasound (R-EBUS)
        ii. N=886 electromagnetic navigation bronchoscopy (ENB)
        iii. 4 RTCs. 38 prospective or retrospective case series
    b. Overall sensitivity to detect cancer was 70.7% [95% confidence interval (CI): 67.2-74.0]; R-EBUS 70.5% (95% CI: 66.1-74.8), ENB 70.7% (95% CI: 64.7-76.8). The overall NPV for cancer was 44.6% (95% CI: 37.9-51.3), R-EBUS 38.3% (95% CI: 31.3-45.4), ENB 53.5% (95% CI: 41.2-65.8).

c. Meta-analysis demonstrated a successful peripheral lung lesion localization rate overall of 93.5% (95% CI: 90.6-96.4), R-EBUS 90.2% (95% CI: 85.6-94.7), ENB 98.2% (95% CI: 96.9-99.4).
d. Pooled overall diagnostic yield was 71.1% (95% CI: 67.3-74.9), R-EBUS 69.1% (95% CI: 64.4-73.7), ENB 73.9% (95% CI: 67.3-80.5).
e. Pooled overall diagnostic accuracy was 74.2% (95% CI: 71.0-77.3); R-EBUS 72.4% (95% CI: 68.7-76.1), ENB 76.4% (95% CI: 70.8-82.0).
f. Biopsy of peripheral nodules caused 58 pneumothoraces/collapsed lung (28 R-EBUS and 30 ENB) in 3056 (1937 R-EBUS, 1119 ENB) procedures: 2% (95% CI: 1.5-2.5), R-EBUS 1.5% (95% CI: 1.0-2.1), ENB 2.7% (95% CI: 1.9-3.8).
g. Conclusion: Both technologies have a high proportion of successful PPL localization with similar sensitivity for malignancy and accuracy

Submitted literature:

1) **Folch 2022**, NAVIGATE 24 month results: electromagnetic navigation bronchoscopy for pulmonary lesions
    a. Single arm pragmatic cohort study (N=1388 enrolled, N=1374 with 1 month follow-up, N=1121 with 12 month follow-up, N=900 with 24 month follow-up)
    b. The primary end point was the incidence of procedure-related pneumothorax grade 2 or higher (requiring intervention or hospitalization)
    c. Total 24-month mortality was 29% (403 of 1388), accounting for most subjects with incomplete follow-up. Furthermore, 16 subjects who died completed the 24-month follow-up and 387 did not. Two-year mortality in subjects with confirmed lung malignancy (true positives plus FNs) was 35.5% (305 of 858).
    d. On the study primary end point, procedure-related pneumothorax Common Terminology Criteria for Adverse Events grade greater than or equal to 2 occurred in 3.2% (44 of 1388) of subjects (5.1% EU, 2.9% U.S.). Any-grade pneumothorax occurred in 4.7% (7.4% EU, 4.3% U.S.). Bronchopulmonary hemorrhage grade 2 or higher occurred in 1.7% (2.3% EU, 1.6% U.S.) and any-grade bronchopulmonary hemorrhage in 2.7% (4.0% EU, 2.5% U.S.). Respiratory failure (grade ≥ 4) occurred in 0.6% (8 subjects, all U.S.), including one death related to complications of general anesthesia 9 days post-ENB in a subject with multiple comorbidities
    e. Among the 1329 subjects undergoing ENB-guided biopsy, 94.8% (1260 of 1329) had navigation completed and tissue obtained. Malignancy was diagnosed in 42.6% (537 of 1260), and 57.4% (723 of 1260) were negative for malignancy on the basis of the ENB-aided procedure
    f. The global diagnostic yield was 67.8% (822 of 1212).
    g. Repeat biopsy after the index ENB procedure (e.g., repeat ENB, surgical biopsy, TTNA, standard bronchoscopy, or EBUS-guided bronchoscopy) was conducted in 26.5% (334 of 1260).
    h. Although ENB has traditionally had a lower diagnostic success rate than percutaneous biopsy, it has a lower complication risk and also allows for the biopsy of multiple nodules and mediastinal staging in the same procedure
    i. Conclusions: ENB demonstrates low complications and a 67.8% diagnostic yield while allowing biopsy, staging, fiducial placement, and dye marking in a single procedure

Computer Assisted Bronchoscopy 2023 Review

Expert guidelines:

1) **NCCN 3.2023** Non-Small Cell Lung Cancer
    a. Diagnostic tools that provide important additional strategies for biopsy include:
        i. EBUS–guided biopsy
        ii. EUS–guided biopsy
        iii. Navigational bronchoscopy
        iv. Robotic bronchoscopy
    b. The least invasive biopsy with the highest yield is preferred as the first diagnostic study:
        i. Patients with central masses and suspected endobronchial involvement should undergo bronchoscopy.
        ii. Patients with peripheral (outer one-third) nodules may benefit from navigational bronchoscopy, radial EBUS, or transthoracic needle aspiration (TTNA).
        iii. Patients with suspected nodal disease should be biopsied by EBUS, EUS, navigational bronchoscopy, or mediastinoscopy.

Other payer policies:

1) Anthem BCBS 2023
    a. Navigational bronchoscopy is considered **medically necessary** for the following indications (A or B):
        i. In individuals for whom nonsurgical biopsy is indicated when both transthoracic needle biopsy and conventional bronchoscopy are considered inadequate to accomplish the diagnostic or interventional objective; **or**
        ii. For the pre-treatment placement of fiducial markers within lung tumor(s).
2) Aetna 2023
    a. Aetna considers electromagnetic navigation (EN)-guided bronchoscopy medically necessary for individuals with a peripheral pulmonary nodule that requires a pathologic diagnosis and is not accessible by standard bronchoscopy methods or by a transthoracic biopsy approach.
3) PacificSource 2022
    a. PacificSource may consider Electromagnetic Navigation Bronchoscopy (ENB) to be medically necessary when ALL the following criteria is met:
        i. The pulmonary nodule is peripheral or if the pulmonary nodule is central, a failed conventional bronchoscopy with endobronchial ultrasound has been attempted
        ii. Transthoracic needle biopsy cannot be done safely (e.g., nearby lung tissue with significant emphysema, risk of pneumothorax unacceptably high) or transthoracic needle biopsy already attempted without establishing a diagnosis

Expert input:

Dr. Mehta and Dr. Delmonaco had input into drafting the guideline criteria

Computer Assisted Bronchoscopy 2023 Review

HERC staff summary:

Since the last review of computer assisted bronchoscopy/navigational bronchoscopy, two systematic review/meta-analyses have been published that demonstrate a diagnostic accuracy and safety profile similar to bronchoscopy and bronchoscopy with endobronchial ultrasound. Private payers surveyed are covering this test for patients with lesions that are not accessible by transthoracic needle biopsy or conventional bronchoscopy or the patient has undergone one of these procedures without obtaining a diagnosis.

HERC staff recommendation:

1) Add CPT 31627 (Computer assisted bronchoscopy) to the Diagnostic Procedure File
2) Remove CPT 31627 from line 662 and modify GN173 as shown below
3) Add a new diagnostic guideline 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 662

The following Interventions are prioritized on Line 662 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
~~31627~~	~~Computer assisted bronchoscopy~~	~~Insufficient evidence of effectiveness~~	~~March 2021~~

DIAGNOSTIC GUIDELINE DX COMPUTER ASSISTED NAVIGATIONAL BRONCHOSCOPY

Computer assisted navigational bronchoscopy (CPT 31627) is covered for EITHER

1) Patients for whom nonsurgical biopsy is indicated when both transthoracic needle biopsy and conventional bronchoscopy are considered inadequate to accomplish the diagnostic or interventional objective; OR
2) The pre-treatment placement of fiduciary markers within lung tumor(s).

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ORIGINAL ARTICLE

The value of navigation bronchoscopy in the diagnosis of peripheral pulmonary lesions: A meta-analysis

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Keywords
Diagnostic yield; electromagnetic navigation bronchoscopy (ENB); peripheral pulmonary lesions (PPLs); transbronchial lung biopsy (TBLB); virtual bronchoscopic navigation (VBN).

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Abstract

Background: To compare the diagnostic yield of peripheral pulmonary lesions (PPLs) with and without navigation system.

Methods: Studies dating from January 1990 to October 2019 were collected from databases. Diagnostic yield of navigation bronchoscopy and non-navigation bronchoscopy was extracted from comparative studies. Subgroup analysis was adopted to test diagnostic yield variation by lesion size, lobe location of the lesion, distance from the hilum, bronchus sign and nature of the lesion.

Results: In total, 2131 patients from 10 studies were enrolled into the study. Diagnostic yield of navigation bronchoscopy was statistically higher than non-navigation bronchoscopy for PPLs (odds ratio [OR] 1.69, 95% confidence interval [CI] 1.32, 2.18, $P < 0.001$), particularly for PPLs in the peripheral third lung (OR 2.26, 95% CI 1.48, 3.44, $P < 0.001$) and for bronchus sign positive PPLs (OR 2.26, 95% CI 1.21, 4.26, $P = 0.011$). Navigation bronchoscopy had better performance than non-navigation bronchoscopy when PPLs were ≤ 20 mm (OR 2.09, 95% CI 1.44, 3.03, $P < 0.001$). It also elevated diagnostic yield of malignant PPLs (OR 1.67, 95% CI 1.26, 2.22, $P < 0.001$) and PPLs in the bilateral upper lobes (OR 1.50, 95% CI 1.09, 2.08, $P = 0.014$).

Conclusions: Navigation bronchoscopy enhanced diagnostic yield when compared to non-navigation bronchoscopy, particularly for PPLs in the peripheral third lung, PPLs being bronchus sign positive, PPLs ≤ 20 mm, malignant PPLs and PPLs in the bilateral upper lobes.

Key points

The current study provided systematic evaluation on the diagnostic value of navigation bronchoscopy by comparing it with non-navigation bronchoscopy, and exploring the factors affecting the diagnostic yield.

Introduction

Early diagnosis of pulmonary lesions is of great importance to reduce mortality due to lung cancer.[1] When endobronchial lesions can be directly visualized by flexible bronchoscopes, peripheral pulmonary lesions (PPLs), generally defined as lesions surrounded by normal pulmonary parenchyma without any computed tomography (CT) evidence of endobronchial abnormalities, are unlikely to be detected by ordinary bronchoscopes.[2,3] Transthoracic needle aspiration (TTNA) has been recommended for nonsurgical diagnosis of PPLs with a sensitivity of 90%, but the relatively high risk of pneumothorax and other complications has limited its application, in particular when PPLs are small or located far from the chest.[3–6] Flexible bronchoscopic biopsy has a lower risk of occurrence of complications; however, the overall sensitivity of PPLs has previously been reported to be only 69%.[5] Therefore,

The Diagnostic Accuracy and Sensitivity for Malignancy of Radial-Endobronchial Ultrasound and Electromagnetic Navigation Bronchoscopy for Sampling of Peripheral Pulmonary Lesions

Systematic Review and Meta-analysis

Anna L. McGuire, MD, MSc, FRCSC,† Renelle Myers, MD,‡ Kyle Grant, MD, MSc,*† Stephen Lam, MD,‡ and John Yee, MD*†*

Background: **Lung cancer screening with computed tomography chest is identifying peripheral pulmonary lesions (PPLs) suspicious for early-stage lung cancer at increasing rates. Radial-endobronchial ultrasound (R-EBUS) and electromagnetic navigation bronchoscopy (ENB) are 2 methods to sample PPLs to diagnose and treat early lung cancer. ENB has a higher operating financial cost, however, the rationale for its use is possible higher diagnostic accuracy versus R-EBUS.**

Objective: **The objective of this study was to determine the comparative diagnostic accuracy, sensitivity, and negative predictive value for R-EBUS and ENB in sampling PPLs.**

Methods: **A systematic review and meta-analysis were conducted. The Ovid Medline database was queried for original research reporting a diagnostic yield of R-EBUS or ENB for PPLs identified on computed tomography chest suspicious for malignancy. The I^2 statistic assessed study heterogeneity. Random effects models produced pooled estimates of diagnostic accuracy and sensitivity for malignancy. Reasons for heterogeneity were explored with meta-regression. Publication bias and small study effects were assessed.**

Results: **A total of 41 studies involved 2988 lung nodules (R-EBUS 2102, ENB 886) in 3204 patients (R-EBUS 2097, ENB 1107). Overall sensitivity to detect cancer was 70.7% [95% confidence interval (CI): 67.2-74.0]; R-EBUS 70.5% (95% CI: 66.1-74.8), ENB 70.7% (95% CI: 64.7-76.8). Pooled overall diagnostic accuracy was 74.2% (95% CI: 71.0-77.3); R-EBUS 72.4% (95% CI: 68.7-76.1), ENB 76.4% (95% CI: 70.8-82.0). The localization modalities had comparative safety profiles of <2% complications.**

Conclusion: **Both technologies have a high proportion of successful PPL localization with similar sensitivity for malignancy and accuracy. As such, both reasonable options for health care authorities to employ diagnostic algorithms.**

Key Words: radial EBUS, endobronchial ultrasound, electromagnetic navigational bronchoscopy, EBUS, ENA, lung cancer

(*J Bronchol Intervent Pulmonol* 2020;27:106–121)

BACKGROUND

Lung cancer screening programs with computed tomography (CT) chest in Canada and Europe are identifying peripheral pulmonary lesions (PPLs) suspicious for early-stage lung cancer in current and former tobacco smokers at increasing rates.[1–3] Current clinical practice guidelines recommend further diagnostic evaluation for PPLs >8 mm in diameter in these high-risk patients.[4] As shown in the National Lung Screening Trial (NLST), the proportion of false-positive (FP) PPLs on screening CT chest may reach 96.4%. This makes an accurate and safe histologic diagnosis of lung malignancy essential to guide lesion management, identifying those who will benefit from curative-intent surgical lung resection.[5] In addition, a proportion of early-stage lung cancer patients may be medically inoperable due to comorbid medical illness and poor pulmonary function. In these cases, an accurate diagnostic procedure is

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A.L.M. and J.Y.: conceived and designed the study, designed the study. J.Y. and A.L.M.: supervised data collection. A.L.M.: managed and collected the study data. A.L.M. and K.G. analyzed the data. A.L.M., S.L., and R.M.: drafted the manuscript. All authors contributed substantially to its revision. A.L.M.: takes responsibility for the paper as a whole.

Disclosure: There is no conflict of interest or other disclosures.

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ORIGINAL ARTICLE

NAVIGATE 24-Month Results: Electromagnetic Navigation Bronchoscopy for Pulmonary Lesions at 37 Centers in Europe and the United States

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***Disclosure:** The authors declare the following competing interests: Drs. Arenberg, Bansal, Bezzi, Bhadra, Bowling, Christensen, Flandes, Gildea, Hogarth, Khandhar, Krimsky, Lamprecht, Lau, LeMense, Mahajan, Mattingley, Murgu, Murillo, Nead, Pritchett, Singh, and Towe report receiving site payments for study participation from Medtronic. Drs. Folch, Flandes, Gildea, Khandhar, Krimsky, and Murgu report serving on the advisory board or steering committee for Medtronic. Drs. Hood, Lin, Mattingley, and Ms. Wolvers are full-time employees and stockholders of Medtronic. Drs. Bhadra, Bowling, Folch, Hogarth, Khandhar, Krimsky, Lau, LeMense, Mahajan, and Pritchett report receiving consultant fees from Medtronic. Dr. Hogarth reports receiving honoraria from Medtronic. Dr. Bansal reports serving on the speaker's bureau with Medtronic.*

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ABSTRACT

Introduction: Electromagnetic navigation bronchoscopy (ENB) is a minimally invasive, image-guided approach to access lung lesions for biopsy or localization for treatment. However, no studies have reported prospective 24-month follow-up from a large, multinational, generalizable cohort. This study evaluated ENB safety, diagnostic yield, and usage patterns in an unrestricted, real-world observational design.

Methods: The NAVIGATE single-arm, pragmatic cohort study (NCT02410837) enrolled subjects at 37 academic and community sites in seven countries with prospective 24-month follow-up. Subjects underwent ENB using the superDimension navigation system versions 6.3 to 7.1. The prespecified primary end point was procedure-related pneumothorax requiring intervention or hospitalization.

Results: A total of 1388 subjects were enrolled for lung lesion biopsy (1329; 95.7%), fiducial marker placement (272; 19.6%), dye marking (23; 1.7%), or lymph node biopsy (36; 2.6%). Concurrent endobronchial ultrasound-guided staging occurred in 456 subjects. General anesthesia (78.2% overall, 56.6% Europe, 81.4% United States), radial endobronchial ultrasound (50.6%, 4.0%, 57.4%), fluoroscopy (85.0%, 41.7%, 91.0%), and rapid on-site evaluation use (61.7%, 17.3%, 68.5%) differed between regions. Pneumothorax and bronchopulmonary hemorrhage occurred in 4.7% and 2.7% of subjects, respectively (3.2% [primary end point] and 1.7% requiring intervention or hospitalization). Respiratory failure occurred in 0.6%. The diagnostic yield was 67.8% (range: 61.9%–70.7%; 55.2% Europe, 69.8% United States). Sensitivity for malignancy was 62.6%. Lung cancer clinical stage was I to II in 64.7% (55.3% Europe, 65.8% United States).

Conclusions: Despite a heterogeneous cohort and regional differences in procedural techniques, ENB demonstrates low complications and a 67.8% diagnostic yield while allowing biopsy, staging, fiducial placement, and dye marking in a single procedure.

Keywords: Interventional pulmonology; Image-guided biopsy; Lung cancer diagnosis; Lung cancer; Electromagnetic navigation bronchoscopy

Introduction

Although lung cancer is the leading cause of cancer-related death in the United States, 5-year survival is substantially higher for cancers diagnosed at localized stages (59%) compared with late-stage diagnoses (6%).[1] Lung cancer screening may further reduce mortality rates[2,3]; however, optimal patient management would ideally minimize the number of invasive procedures conducted for benign disease. In an era of increased scrutiny over resource utilization, technologies with the ability to perform multiple procedures in the same setting and accelerate treatment are also critical to improve the efficiency and effectiveness of lung nodule evaluation. Clinical practice guidelines recommend diagnosis and staging of the mediastinum in a single setting to improve coordination of care and reduce time, cost, and risk.[4]

Image-guided techniques have advanced the field of bronchoscopy in the past 20 years.[5] Minimally invasive options such as radial endobronchial ultrasound (rEBUS) and electromagnetic navigation bronchoscopy (ENB) improve the diagnostic accuracy of bronchoscopy for early stage lung cancer and reduce the need for more invasive surgical procedures.[6] ENB also allows for lung biopsy, tissue collection for molecular testing, mediastinal staging, and fiducial or dye marking to facilitate treatment in the same procedure. Despite those advantages and a reduced complication risk compared with percutaneous lung biopsy,[7] the lower diagnostic yield of ENB is a limitation.

New imaging techniques and robotic navigation platforms have recently emerged with the goal of improving the localization accuracy of ENB and other forms of advanced bronchoscopy.[8–14] As these technologies mature, there is a need to identify which outcomes are generalizable across diverse settings. This requires a solid foundation of evidence in a real-world population against which to compare new devices. Although the safety and effectiveness of ENB-guided

OncoExTra

Plain Language Summary:

Coverage question: Should OHP cover a medical testing that helps figure out the risk for advanced cancer (OncoExTra)?

Should OHP cover this treatment? Yes, staff recommend covering as similar tests using more generic codes are already covered.

Coverage Question: Should the PLA code for OncoExTra be added to the Diagnostic file for testing of cancer tissue?

Question source: Exact Sciences

Background: The OncoExTra (Exact Sciences Inc., Genomic Health Inc.), formerly known as Oncotype Map and GEM ExTra, respectively, is an oncology (neoplasia) test that conducts exome and transcriptome sequence analysis for sequence variants, gene copy number amplifications and deletions, gene rearrangements, microsatellite instability and tumor mutational burden utilizing DNA and RNA from tumor with DNA from normal blood or saliva for subtraction. This test is designed to report clinically significant mutation(s) with therapy associations. Exact Sciences is requesting review of this test.

Previous HERC reviews on cancer tissue have centered on next generation sequencing (NGS) and a new guideline for NGS was added to the Prioritized List at the September 2023 VBBS/HERC meetings. NGS tests generally include about 500 genes for interest. Whole exome testing would provide results of thousands of genes whether or not they are clinically actionable (that is, they are the target for a specific medication). The OncoExtra PLA code states that only clinically significant mutations are reported.

Current coverage for whole exome sequencing is limited to non-prenatal non cancer related genetic testing. The last review of WES was in 2014, and the GAP comment was "Used when there are multiple anomalies in a child, or when other specific testing has not found a diagnosis. 20-30% chance of finding a genetic cause for a syndrome or developmental delay in a population of children who already had non-revealing testing."

Current Prioritized List/Coverage status:

On the Excluded File:
PLA 0329U Oncology (neoplasia), exome and transcriptome sequence analysis for sequence variants, gene copy number amplifications and deletions, gene rearrangements, microsatellite instability and

OncoExTra

tumor mutational burden utilizing DNA and RNA from tumor with DNA from normal blood or saliva for subtraction, report of clinically significant mutation(s) with therapy associations

Similar codes:
PLA 0036U Exome (i.e., somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses

Whole exome codes:
CPT 81415 Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis is currently Diagnostic and covered by Diagnostic Guideline D1 which does not include cancer tissue testing.

Excerpt from DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE

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

DIAGNOSTIC GUIDELINE DX, NEXT GENERATION SEQUENCING OF MALIGNANCIES [EFFECTIVE 1/1/24]

Next Generation Sequencing (NGS, for example CPT 81479, 81455, 0037U) is covered when all of the following requirements are met:

1) The patient has
    a. Either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; AND
    b. Has not been previously tested using the same NGS test for the same primary diagnosis of cancer, unless the criteria in 4) below are met; AND
    c. Decided to seek further cancer treatment (for example, therapeutic chemotherapy) and has adequate performance status (ECOG 0-2) to undergo such treatment; AND
2) The diagnostic laboratory test using NGS must have:
    a. Clinical Laboratory Improvement Amendments (CLIA)-certification; AND
    b. The test is being used as a companion diagnostic test in accordance with Food & Drug Administration (FDA)-approved therapeutic labeling; AND
    c. Results provided to the treating physician for management of the patient using a report template to specify treatment options; AND
3) A single CPT or HCPCS code is covered for each multigene panel performed on tumor tissue. Additional codes for individual genes and for molecular pathology procedures CPT 81400-81408 are excluded from coverage when the multigene panel is covered under the appropriate CPT or HCPCS code.
4) Repeat NGS testing may be required in the setting of patients who have clinically progressed per standardized professional guidelines after therapy. Coverage in this situation is limited to 3 times per primary malignancy unless there is indication for additional testing after individualized review of medical necessity.

Expert guidelines:

1) American Society for Clinical Oncology (ASCO) 2022, Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer

OncoExTra

a. Expert consensus
    i. When tumor mutation burden (TMB) may influence the decision to use immunotherapy, testing should be performed with either large multigene panels with validated TMB testing or whole-exome analysis (strength of recommendation: strong).
        1. TMB refers to the number of somatic mutations per megabase of DNA sequenced and often varies from tumor type to tumor type
        2. In 2020, pembrolizumab was approved in its second tumor agnostic indication for the treatment of adult and pediatric patients with unresectable or metastatic, high TMB (defined as ≥ 10 mutations per Mb) solid tumors on the basis of the single-arm KEYNOTE-158 study of 129 patients across 10 different cancer types that demonstrated a 29% ORR in the high TMB cohort not fully accounted for by MSI status
        3. The benchmark method to measure TMB is whole-exome sequencing that interrogates approximately 22,000 genes or approximately 30 Mb of coding regions of the genome (ie, approximately 1% of the genome), but clinical whole-exome sequencing is not commonly used. Instead, multigene panel–based sequencing with fewer genes (324-595 genes in currently available panels) and coding regions (0.8-2.4 Mb) is more often used to estimate TMB

Other payer policies:

1) Aetna 2021 considers OncoExTra to be experimental
2) Regence BCBS 2023
    a. Whole exome sequencing is considered investigational for the diagnosis of genetic disorders when Criterion I [evaluation of neurodevelopmental disorders in pediatric patients] is not met, including but not limited to…testing for cancer treatment selection.
3) United HealthCare 2023
    a. Any other CGP test for solid tumors not addressed above (e.g., oncomap™ ExTra, NeoTYPE® Discovery Profile for Solid Tumors, MSK-IMPACT® , TheraMap™ Solid Tumor, CANCERPLEX® , Solid Tumor Profile Plus, Tempus xT) is considered unproven and not medically necessary for use as a companion diagnostic due to insufficient evidence of efficacy
4) Anthem BCBS 2022
    a. Covers molecular profiling (whole genome, whole exome, and gene panels) for unresectable or metastatic solid tumors when all of the criteria below are met:
        i. The test is used to assess tumor mutation burden and identify candidates for checkpoint inhibition immunotherapy
        ii. Individual has progressed following prior treatment
        iii. Individual has no satisfactory alternative treatment options
    b. Tests covered: 81445, 0037U [FoundationOne CDx], 0211U [Caris Life Sciences], 0244U, 0250U, 0334U

OncoExTra

HERC staff summary:

Review and discussion to date on testing for cancer tissue has centered around panel testing. Panel tests, such as FoundationOneCDx (PLA 0037U), Caris Life Sciences (CPT 81445) and Knight Cancer Labs GeneTrails (CPT 81479). Panel tests typically include approximately 500 genes known to be actionable, defined as a companion diagnostic test to an FDA approved chemotherapy agent. OncoExTra would test for many more than 500 genes. Most private payers surveyed consider this test to be experimental.

Whole exome sequencing of cancer tissue is strongly recommended by ASCO for patients with advanced or metastatic cancer when the test is used to assess tumor mutation burden and identify candidates for checkpoint inhibition immunotherapy. Anthem BCBS covers this testing for this indication, in patients who have progressed following prior treatment and have no satisfactory alternative treatment options.

HERC staff recommendations:

1) Place PLA 0329U (Oncology (neoplasia), exome and transcriptome sequence analysis for sequence variants, gene copy number amplifications and deletions, gene rearrangements, microsatellite instability and tumor mutational burden utilizing DNA and RNA from tumor with DNA from normal blood or saliva for subtraction, report of clinically significant mutation(s) with therapy associations) on the Diagnostic Procedures File
2) Modify the new guideline on cancer genetic sequencing panels as shown below
    a. Edits recommended in another issue summary are shown in purple

DIAGNOSTIC GUIDELINE DX, NEXT GENERATION SEQUENCING OF MALIGNANCIES

Next Generation Sequencing (NGS, for example CPT 81479, 81455, 0037U) is covered when all of the following requirements are met:

1) The patient has
    a. ~~Either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer~~ a tissue diagnosis confirming cancer and has been evaluated by an oncologist or oncologic surgeon; AND
    b. Has not been previously tested using the same NGS test for the same primary diagnosis of cancer, unless the criteria in 4) below are met; AND
    c. Decided to seek further cancer treatment (for example, therapeutic chemotherapy) and has adequate performance status (ECOG 0-2) to undergo such treatment; AND
2) The diagnostic laboratory test using NGS must have:
    a. Clinical Laboratory Improvement Amendments (CLIA)-certification; AND
    b. The test is being used as a companion diagnostic test in accordance with Food & Drug Administration (FDA)-approved therapeutic labeling; AND
    c. Results provided to the treating physician for management of the patient using a report template to specify treatment options; AND
3) A single CPT or HCPCS code is covered for each multigene panel performed on tumor tissue. Additional codes for individual genes and for molecular pathology procedures CPT 81400-81408 are excluded from coverage when the multigene panel is covered under the appropriate CPT or HCPCS code.
4) Repeat NGS testing may be required in the setting of patients who have clinically progressed per standardized professional guidelines after therapy. Coverage in this situation is limited to 3 times per primary malignancy unless there is indication for additional testing after individualized review of medical necessity.

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5) Whole exome sequencing of cancer tissue (for example, 0329U or 0211U) is covered ONLY when all of the following criteria are met:
    a. The patient has advanced or metastatic cancer; AND
    b. The test is used to assess tumor mutation burden and identify candidates for checkpoint inhibition immunotherapy; AND
    c. The patient has progressed following prior treatment; AND
    d. There are no satisfactory alternative treatment options.

Commented [JG1]: Testing options? Or options besides checkpoint inhibition immunothersapy?

Commented [SA2R1]: Treatment other than checkpoint inhibition

ASCO special articles

Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion

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abstract

PURPOSE An ASCO provisional clinical opinion offers timely clinical direction to ASCO's membership following publication or presentation of potentially practice-changing data from major studies. This provisional clinical opinion addresses the appropriate use of tumor genomic testing in patients with metastatic or advanced solid tumors.

CLINICAL CONTEXT An increasing number of therapies are approved to treat cancers harboring specific genomic biomarkers. However, there is a lack of clarity as to when tumor genomic sequencing should be ordered, what type of assays should be performed, and how to interpret the results for treatment selection.

PROVISIONAL CLINICAL OPINION Patients with metastatic or advanced cancer should undergo genomic sequencing in a certified laboratory if the presence of one or more specific genomic alterations has regulatory approval as biomarkers to guide the use of or exclusion from certain treatments for their disease. Multigene panel–based assays should be used if more than one biomarker-linked therapy is approved for the patient's disease. Site-agnostic approvals for any cancer with a high tumor mutation burden, mismatch repair deficiency, or neurotrophic tyrosine receptor kinase (*NTRK*) fusions provide a rationale for genomic testing for all solid tumors. Multigene testing may also assist in treatment selection by identifying additional targets when there are few or no genotype-based therapy approvals for the patient's disease. For treatment planning, the clinician should consider the functional impact of the targeted alteration and expected efficacy of genomic biomarker–linked options relative to other approved or investigational treatments.

Additional information is available at www.asco.org/assays-and-predictive-markers-guidelines.

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INTRODUCTION

Multigene panels for next-generation sequencing (NGS) are now US Food and Drug Administration (FDA)-approved in several tumor types.[1] In 2020 alone, 28 targeted therapies were approved by the FDA in patient populations defined by specific molecular biomarkers,[2] and many clinical trials now often use genomic sequencing to define patient eligibility. The population of patients who may benefit from genomic sequencing expanded with the approval of the anti–programmed death-1 (anti-PD1) antibody, pembrolizumab, in all mismatch repair deficient (dMMR) solid tumors[3] and with cancer site–agnostic approvals of pembrolizumab and larotrectinib in tumor mutation burden-high (TMB-H)[4] and neurotrophic tyrosine receptor kinase (*NTRK*) fusion–positive solid tumors,[4] respectively.

The interpretation of genomic sequencing data is complex. Not all tumors have alterations within therapeutically targetable or actionable genes, and not all alterations detected within a therapeutically actionable gene may confer sensitivity to genomic biomarker–linked therapies. Many alterations in actionable genes do not alter gene function, and many agents are only active against specific alterations. Basket trials enrolling multiple tumor types with the same or similar genomic alterations have shown that responses to the same genomic alteration may vary among tumor types.[5-7] Information from paired tumor and germline analyses and knowledge of co-occurring alterations, mutational heterogeneity, and subclonal mutations add to the complexity of interpreting genomic sequencing.[8]

ASCO has convened an expert panel to provide guidance on using genomic sequencing to inform treatment selection for patients with metastatic or advanced solid tumors. The neoadjuvant and adjuvant treatment settings were specifically excluded from the scope of the project as were patients with nonsolid tumors (eg, lymphoma). The panel recognizes that

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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Section 9.0

New Codes

Code	Description	Information/Similar codes	Code Placement Recommendation
27278	Arthrodesis, sacroiliac joint, percutaneous, with image guidance, including placement of intra-articular implant(s) (eg, bone allograft[s], synthetic device[s]), without placement of transfixation device	Similar code 27279 (Arthrodesis, sacroiliac joint, percutaneous or minimally invasive (indirect visualization), with image guidance, includes obtaining bone graft when performed, and placement of transfixing device) is on lines 183,398,530 govered by GN 161 SACROILIAC JOINT INJECTIONS AND SACROILIAC JOINT FUSION	183 FRACTURE OF PELVIS, OPEN AND CLOSED 398 SEVERE SACROILIITIS 530 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS
61889	Insertion of skull-mounted cranial neurostimulator pulse generator or receiver, including craniectomy or craniotomy, when performed, with direct or inductive coupling, with connection to depth and/or cortical strip electrode array(s)	Similar code 61885 (Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array) is on lines 174,249,285	174 GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY WITHOUT MENTION OF IMPAIRMENT OF CONSCIOUSNESS 249 PARKINSON'S DISEASE
61891	Revision or replacement of skull-mounted cranial neurostimulator pulse generator or receiver with connection to depth and/or cortical strip electrode array(s)	See 61889	174 GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY WITHOUT MENTION OF IMPAIRMENT OF CONSCIOUSNESS 249 PARKINSON'S DISEASE 285 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT

Code	Description	Information/Similar codes	Code Placement Recommendation
61892	Removal of skull-mounted cranial neurostimulator pulse generator or receiver with cranioplasty, when performed	See 61889	174 GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY WITHOUT MENTION OF IMPAIRMENT OF CONSCIOUSNESS 249 PARKINSON'S DISEASE 285 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT
64596	Insertion or replacement of percutaneous electrode array, peripheral nerve, with integrated neurostimulator, including imaging guidance, when performed; initial electrode array	Similar code 64590 (Insertion or replacement of peripheral or gastric neurostimulator pulse generator or receiver, direct or inductive coupling) in on lines 327,457,529. 64590 is modified to specify "requiring pocket creation and connection between electrode array and pulse generator or receiver"	327 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION 457 URINARY INCONTINENCE 529 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS
64597	Insertion or replacement of percutaneous electrode array, peripheral nerve, with integrated neurostimulator, including imaging guidance, when performed; each additional electrode array (List separately in addition to code for primary procedure)	See 64596	327 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION 457 URINARY INCONTINENCE 529 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS

Code	Description	Information/Similar codes	Code Placement Recommendation
64598	Revision or removal of neurostimulator electrode array, peripheral nerve, with integrated neurostimulator	Similar code 64595 (Revision or removal of peripheral or gastric neurostimulator pulse generator or receiver) is on lines 285 and 424. 64595 is modified to specify "with detachable connection to electrode array"	285 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 424 COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT
75580	Noninvasive estimate of coronary fractional flow reserve (FFR) derived from augmentative software analysis of the data set from a coronary computed tomography angiography, with interpretation and report by a physician or other qualified health care profes	FFR was reviewed in May 2022 and CPT 0501T-0504T were added to the Diagnostic Procedure File	Diagnostic Procedures File
76984	Ultrasound, intraoperative thoracic aorta (eg, epiaortic), diagnostic	other vascular ultrasound codes are on the Diagnostic Procedures file	Diagnostic Procedures File
76987	Intraoperative epicardial cardiac ultrasound (ie, echocardiography) for congenital heart disease, diagnostic; including placement and manipulation of transducer, image acquisition, interpretation and report	ECHO codes are all Diagnostic, and intraoperative ECHO appears to be standard of care for certain cardiac procedures	Diagnostic Procedures File
76988	Intraoperative epicardial cardiac ultrasound (ie, echocardiography) for congenital heart disease, diagnostic; placement, manipulation of transducer, and image acquisition only	See 76987	Diagnostic Procedures File
76989	Intraoperative epicardial cardiac ultrasound (ie, echocardiography) for congenital heart disease, diagnostic; interpretation and report only	See 76987	Diagnostic Procedures File

Code	Description	Information/Similar codes	Code Placement Recommendation
82166	Anti-mullerian hormone (AMH)	Used in infertility testing; used to test for early menopause; used for monitoring certain types of ovarian cancer; used for work up of atypical genitalia and for work up of undescended testes	Diagnostic Procedures File
86041	Acetylcholine receptor (AChR); binding antibody	Used to diagnose myasthenia gravis	Diagnostic Procedures File
86042	Acetylcholine receptor (AChR); blocking antibody	Used to diagnose myasthenia gravis	Diagnostic Procedures File
86043	Acetylcholine receptor (AChR); modulating antibody	Used to diagnose myasthenia gravis	Diagnostic Procedures File
86366	Muscle-specific kinase (MuSK) antibody	Used to diagnose myasthenia gravis when acetylcholine receptor testing is negative	Diagnostic Procedures File
87523	Infectious agent detection by nucleic acid (DNA or RNA); hepatitis D (delta), quantification, including reverse transcription, when performed	Antibody testing for hepatisis D (CPT 86692) is Diagnostic. Detection of other hepatitis viruses by DNA or RNA testing is Diagnostic	Diagnostic Procedures File
87593	Infectious agent detection by nucleic acid (DNA or RNA); Orthopoxvirus (eg, monkeypox virus, cowpox virus, vaccinia virus), amplified probe technique, each	Detection of other viruses by DNA or RNA testing is Diagnostic	Diagnostic Procedures File
90380	Respiratory syncytial virus, monoclonal antibody, seasonal dose; 0.5 mL dosage, for intramuscular use		Added to line 3 at the September 2023 HERC meeting
90381	Respiratory syncytial virus, monoclonal antibody, seasonal dose; 1 mL dosage, for intramuscular use		Added to line 3 at the September 2023 HERC meeting

Code	Description	Information/Similar codes	Code Placement Recommendation
90589	Chikungunya virus vaccine, live attenuated, for intramuscular use	There is currently no FDA approved vaccine for Chikungunya virus	Excluded File (This virus is set to be reviewed by ACIP in 2024)
90611	Smallpox and monkeypox vaccine, attenuated vaccinia virus, live, non-replicating, preservative free, 0.5 mL dosage, suspension, for subcutaneous use		Added to line 3 in August 2022
90622	Vaccinia (smallpox) virus vaccine, live, lyophilized, 0.3 mL dosage, for percutaneous use		Added to line 3 in August 2022
90623	Meningococcal pentavalent vaccine, conjugated Men A, C, W, Y- tetanus toxoid carrier, and Men B-FHbp, for intramuscular use	FDA and ACIP have approved Pfizer's MenABCWY vaccine as of October 2023	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
90679	Respiratory syncytial virus vaccine, preF, recombinant, subunit, adjuvanted, for intramuscular use		Added to line 3 at the September 2023 HERC meeting
90683	Respiratory syncytial virus vaccine, mRNA lipid nanoparticles, for intramuscular use		Added to line 3 at the September 2023 HERC meeting
92622	Diagnostic analysis, programming, and verification of an auditory osseointegrated sound processor, any type; first 60 minutes	Implantation of osseointegrated implants (CPT 69716) is on lines 311 and 446	311 HEARING LOSS - AGE 5 OR UNDER 446 HEARING LOSS - OVER AGE OF FIVE
92623	Diagnostic analysis, programming, and verification of an auditory osseointegrated sound processor, any type; each additional 15 minutes (List separately in addition to code for primary procedure)	Implantation of osseointegrated implants (CPT 69716) is on lines 311 and 446	311 HEARING LOSS - AGE 5 OR UNDER 446 HEARING LOSS - OVER AGE OF FIVE

Code	Description	Information/Similar codes	Code Placement Recommendation
93584	Venography for congenital heart defect(s), including catheter placement, and radiological supervision and interpretation; anomalous or persistent superior vena cava when it exists as a second contralateral superior vena cava, with native drainage to heart	Per AMA, these codes are to be used as an add on code with congenital heart catheterization codes (93593, 93594, 93595, 93596, 93597) which are on 21 lines containing congenital heart disease diagnoses	45 CORONARY ARTERY ANOMALY 67 VENTRICULAR SEPTAL DEFECT 70 CONGENITAL PULMONARY VALVE ANOMALIES 76 PATENT DUCTUS ARTERIOSUS; AORTIC PULMONARY 84 ENDOCARDIAL CUSHION DEFECTS 85 CONGENITAL PULMONARY VALVE ATRESIA 88 DISCORDANT CARDIOVASCULAR CONNECTIONS 89 CONGENITAL MITRAL VALVE STENOSIS/INSUFFICIENCY 104 ETRALOGY OF FALLOT (TOF); CONGENITAL VENOUS ABNORMALITIES 105 CONGENITAL STENOSIS AND INSUFFICIENCY OF AORTIC VALVE 110 CONGENITAL HEART BLOCK; OTHER OBSTRUCTIVE ANOMALIES OF HEART 118 ATRIAL SEPTAL DEFECT, SECUNDUM 128 COMMON TRUNCUS 130 TOTAL ANOMALOUS PULMONARY VENOUS CONNECTION 134 INTERRUPTED AORTIC ARCH
93585	Venography for congenital heart defect(s), including catheter placement, and radiological supervision and interpretation; azygos/hemiazygos venous system (List separately in addition to code for primary procedure)	See 93584	45, 67, 70, 76, 84, 85, 88, 89, 104, 105, 110, 118, 128, 130, 134, 138, 176, 188, 232, 264, 653

Code	Description	Information/Similar codes	Code Placement Recommendation
93586	Venography for congenital heart defect(s), including catheter placement, and radiological supervision and interpretation; coronary sinus (List separately in addition to code for primary procedure)	See 93584	45, 67, 70, 76, 84, 85, 88, 89, 104, 105, 110, 118, 128, 130, 134, 138, 176, 188, 232, 264, 653
93587	Venography for congenital heart defect(s), including catheter placement, and radiological supervision and interpretation; venovenous collaterals originating at or above the heart (eg, from innominate vein) (List separately in addition to code for primary	See 93584	45, 67, 70, 76, 84, 85, 88, 89, 104, 105, 110, 118, 128, 130, 134, 138, 176, 188, 232, 264, 653
93588	Venography for congenital heart defect(s), including catheter placement, and radiological supervision and interpretation; venovenous collaterals originating below the heart (eg, from the inferior vena cava) (List separately in addition to code for primary	See 93584	45, 67, 70, 76, 84, 85, 88, 89, 104, 105, 110, 118, 128, 130, 134, 138, 176, 188, 232, 264, 653

Plain Language Summary:

Coverage question: Should OHP cover a medical process to attach a device to the bones of the spine to treat abnormal curves of the spine?

Should OHP cover this treatment? No, the risks for this process are too high and it is considered not yet proven (experimental) by private insurance.

Codes:

1) **22836** Anterior thoracic vertebral body tethering, including thoracoscopy, when performed; up to 7 vertebral segments
2) **22837** 8 or more vertebral segments
3) **22838** Revision (eg, augmentation, division of tether), replacement, or removal of thoracic vertebral body tethering, including thoracoscopy, when performed

Information: Anterior vertebral body tethering is a surgical treatment for scoliosis. Scoliosis is an abnormal lateral and rotational curvature of the spin. Standard treatments for scoliosis includes bracing and spinal fusion. The tethering procedure is being evaluated as a procedure that can reduce the rate of spine growth unilaterally, allowing the other side of the spine to "catch up." Anterolateral tethering uses polyethylene ligaments that are attached to the convex side of the vertebral bodies by pedicle screws or staples. The ligament can be tightened to provide greater tension than the staple. The vertebral Body Tethering System™ is indicated for skeletally immature patients that require surgical treatment to obtain and maintain correction of progressive idiopathic scoliosis. This technology was approved in 2019 by the FDA under a Humanitarian Device Exception.

Evidence

NICE 2022, evidence review for vertebral body tethering for idiopathic scoliosis in children and young people

1. In a meta-analysis of 24 studies (n=1,280: 1,278 patients with idiopathic scoliosis and 2 patients with syndromic scoliosis), the pooled mean Cobb angle of the main thoracic curve was 46.0° (95% CI 42.3° to 50.0°; 10 studies) in patients who had anterior vertebral body tethering (VBT) and 53.3° (95% CI 52.8° to 53.9°; 14 studies) in patients who had posterior spinal fusion (PSF) preoperatively. Of the studies with a follow up of 36 months or more after operation (number of studies not reported), the mean main thoracic curve was corrected to 22.5° (95% CI 14.1° to 30.9°) for anterior VBT and 22.7° (95% CI 19.6° to 25.8°) for PSF. In the same meta-analysis, the pooled mean Cobb angle of the lumbar curve was 28.7° (95% CI 25.6° to 32.0°; 9 studies) for anterior VBT and 30.9° (95% CI 29.2° to 32.5°; 5 studies) for PSF preoperatively. This was corrected to 18.0° (95% 3.5° to 32.5°) and 15.2° (13.3° to 17.1°) at a follow up of 36 months or more (number of studies not reported; Shin 2021)

2. In the meta-analysis of 24 studies (n=1,280), the mean thoracic rotation was 13.7° (95% CI 12.1° to 15.2°; 6 studies) in patients who had anterior VBT and 15.4° (95% CI 12.4° to 18.4°; 3 studies) in patients who had PSF preoperatively. After operation, thoracic rotation changed to 8.4° (95% CI 1.0° to 15.7°) with anterior VBT and 13.0° (95% CI 3.3° to 22.6°) with PSF at a follow up of 36 months or more (number of studies not reported; Shin 2021).
3. In the meta-analysis of 24 studies (n=1,280), there was no statistically significant difference found in the postoperative SRS-22 self-image or total scores between patients who had anterior VBT and patients who had PSF (self-image, 4.27 [95% CI 4.0 to 4.56; 2 studies] compared with 4.23 [95% CI 4.07 to 4.40; 7 studies]; total score, 4.36 [95% CI 4.06 to 4.65; 2 studies] compared with 4.30 [95% CI4.17 to 4.43; 7 studies]; Shin 2021)
4. The pooled complication rate was 26% (95% CI 12% to 40%, I2=86.14%; 10 studies) in patients who had anterior VBT and 2% (95% CI 0% to 4%, I2=19.21%; 9 studies) in patients who had PSF in the meta-analysis of 24 studies (n=1,280).

Raitio 2022, systematic review of vertebral body tethering

1. N=23 studies (843 patients), minimum follow up 2 years

a. All registry or cohort studies

2. In the included studies, the mean preoperative main thoracic curve was 49 degrees, which corrected to 24 degrees in first postoperative imaging. VBT provided sustainable median-term results as the reported curves after a minimum of two-year follow-up averaged at 23 degrees
3. In the included studies, the complication rate was 18% with pulmonary (pneumothorax, pleural effusion) and instrumentation-related (tether breakage, overcorrection) being the most common. Reoperations related to tethering were required in 10% of cases. These included tether release(s) for overcorrection, replacing and extending tethers for breakage or curve progression, and chest tube insertions for pulmonary complications. The vast majority avoided spinal fusion, as only 4.7% of VBT patients required conversion to PSF after unsuccessful tethering.
4. There was only one study comparing traditional fusion and AVBT. Newton et al. compared the outcomes of AVBT and PSF using pedicle screw instrumentation at a mean of 3.5 years follow-up. The correction of major thoracic curves was significantly better in the PSF group (70%) as compared with AVBT (38%). There were nine revisions in the AVBT group including three conversions into PSF with three more pending. Twelve patients had a broken tether, but the majority (74%) of the patients in the AVBT cohort had avoided spinal fusion at the end of follow-up.
5. Conclusion: While the reported median-term results of VBT appear promising, long-term results of this technique are currently lacking

<u>Expert guidelines</u>

1) **Pediatric Orthopaedic Society of North America/Scoliosis Research Society** joint position statement on anterior fusionless scoliosis technologies for immature patients with idiopathic scoliosis

a. In summary, a wide variety of centers and surgeons across the US, Canada, and outside North America have reproduced clinical results demonstrating acceptable safety and efficacy of anterior vertebral body tethering (AVBT) in skeletally immature patients. The FDA has judged this treatment as 'safe' and with 'probable benefit', and given this FDA approval the SRS and POSNA support insurance payor coverage for FDA approved usage of such devices

Other payer policies

1) NICE 2022: Evidence on the safety of vertebral body tethering for idiopathic scoliosis in children and young people is limited but raises concerns of serious complications. Evidence on its efficacy is inadequate in quality and quantity. Therefore, this procedure should only be used in the context of research.
2) United Health Care 2023: Vertebral body tethering for the treatment of scoliosis is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy
3) Aetna 2023 considers vertebral body tethering to be experimental
4) Cigna 2023 considers vertebral body tethering for adolescent idiopathic scoliosis to be experimental

HERC staff summary

The literature to date for vertebral body tethering for scoliosis consists of cohorts studies, registry studies, and case series. There appears to be only one study directly comparing this technology to other surgical interventions, and no studies comparing it to bracing. There appears to be a high rate of complications from this procedure. One highly regarded evidence-based guideline (NICE 2022) recommends against coverage. Private payers surveyed are currently not covering this procedure as experimental.

HERC staff recommendations:

1) Place vertebral body tethering CPT codes on line 662 and
   a. **22836** Anterior thoracic vertebral body tethering, including thoracoscopy, when performed; up to 7 vertebral segments
   b. **22837** 8 or more vertebral segments
   c. **22838** Revision (eg, augmentation, division of tether), replacement, or removal of thoracic vertebral body tethering, including thoracoscopy, when performed
2) Add an entry to GN173 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 662

The following Interventions are prioritized on Line 662 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
22836-22838	Anterior thoracic vertebral body tethering	Insufficient evidence of effectiveness	November 2023

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of vertebral body tethering for idiopathic scoliosis in children and young people

Scoliosis is the abnormal sideways curving of the spine, which in most cases has an unknown cause (idiopathic). It usually develops in childhood and early adolescence and can lead to deformity of the chest wall. In this procedure, under general anaesthesia, screws are put into the vertebral bodies (bone discs that make up the spine). A cord is fixed (tethered) to the screws and pulled taut restricting growth on the long side. This allows the spine to grow faster on the short side so that the curve is gradually corrected. The aim is to correct the scoliosis before the person reaches adulthood and their spine stops growing.

Contents

Journal of
Clinical Medicine

MDPI

Review

Vertebral Body Tethering: Indications, Surgical Technique, and a Systematic Review of Published Results

Arimatias Raitio [1], Johanna Syvänen [2] and Ilkka Helenius [3,*]

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Abstract: Vertebral body tethering (VBT) represents a new surgical technique to correct idiopathic scoliosis using an anterior approach, spinal instrumentation with vertebral body screws, and a cable compressing the convexity of the curve. According to the Hueter-Volkmann principle, compression reduces and distraction increases growth on the growth plates. VBT was designed to modulate spinal growth of vertebral bodies and hence, the term 'growth modulation' has also been used. This review describes the indications and surgical technique of VBT. Further, a systematic review of published studies was conducted to critically evaluate the results and complications of this technique. In a total of 23 included studies on 843 patients, the preoperative main thoracic curve corrected from 49 to 23 degrees in a minimum 2 year follow-up. The complication rate of VBT was 18%. The results showed that 15% of VBT patients required reoperations for pulmonary or tether-related issues (10%) and less than 5% required conversion to spinal fusion. While the reported median-term results of VBT appear promising, long-term results of this technique are currently lacking.

Keywords: adolescent idiopathic scoliosis; growth-friendly techniques; surgery; vertebral body tethering

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1. Introduction

Adolescent idiopathic scoliosis (AIS) is a three-dimensional deformity including a lateral deviation of the spine, reduced thoracic kyphosis, and rotation of the vertebral bodies. A curve of 45 degrees or higher is typically regarded as an indication to surgical treatment as these curves typically continue to progress even in skeletally mature patients [1]. Additionally, thoracic curves of over 50 degrees are associated with reduced lung volumes [2].

Three-dimensional correction of scoliosis and continued growth should be the aim of the treatment of spinal deformity on a growing child [3]. Posterior spinal fusion with pedicle screw instrumentation has been the traditional method to address these curves [4]. Normal lung development is dependent on the length of the thoracic spine and its final length is closely related to the lung volume obtained at skeletal maturity [5]. A recommended minimum length of the thoracic spine before posterior fusion is 22 cm [6–8]. Additional length obtained from correction of spinal deformity averages about 25 mm in normal AIS [9].

Spinal fusion provides sustainable long-term outcomes but is associated with reduced spinal mobility [10] and hence reduced functional outcomes as compared with the normal population [11]. On the other hand, it leads to an irreversible stage of permanent spinal fusion and straining of the remaining mobile segment due to reduced spinal mobility [12,13]. These disadvantages have led surgeons to investigate other methods to correct adolescent idiopathic scoliosis without spinal fusion.

to be effectively treated with AVBT with low complication rate and low rate of revision surgery at 2 years post-operative.

At SRS 2018, Turcot et al. presented their results of a prospective developmental study of 23 patients with 2 years follow-up[25]. The average age at time of surgery was 11.8 years. Mean thoracic Cobb 53° improved to 27° at most recent follow-up. Thoracic kyphosis was found to be unchanged from preoperative radiographs and most recent follow-up. Apical vertebral rotation corrected on average from 14° to 11° at most recent follow-up. This abstract showed there is progressive improvement of coronal and rotational deformity.

At POSNA 2019, Miyanji et al. presented an AVBT study with the largest patient cohort to date[26]. They conducted a prospective multicenter database study of AVBT with minimum 2-year follow-up in 57 patients who underwent a total of 63 procedures. The mean age at time of surgery was 12.7 years and mean follow-up was 29.2 months. Mean preoperative curve improved from 51° to 23° and mean compensatory curve improved a mean 31% at most recent follow-up. In this review of 57 patients from 2 centers, the authors concluded AVBT is an acceptable treatment option being effective at preventing and obtaining curve correction in most patients.

IV. Summary

In summary, a wide variety of centers and surgeons across the US, Canada, and outside North America have reproduced clinical results demonstrating acceptable safety and efficacy of anterior vertebral body tethering (AVBT) in skeletally immature patients. The FDA has judged this treatment as 'safe' and with 'probable benefit', and given this FDA approval the SRS and POSNA support insurance payor coverage for FDA approved usage of such devices. There have been no published scientific reports to support the use of vertebral tethering or other non-fusion anterior instrumentation in treating scoliosis in skeletally mature individuals. **The SRS and POSNA do not support the use or reimbursement for anterior non-fusion instrumentation in skeletally mature individuals for the management of scoliosis or other spinal deformities**. For skeletally immature patients with idiopathic scoliosis who, with their parents/guardians, have selected this approach via shared decision making with their health care professionals considering the risks (including higher rate of reoperation) and the motion preserving benefits, the SRS and POSNA recommend such treatment as an insured covered benefit.

2023 CPT Code Review
Posterior Nasal Nerve Ablation

Plain Language Summary:

Coverage question: Should OHP cover a medical process to destroy a nerve that can cause a constant runny nose?

Should OHP cover this treatment? No. The process is not well-studied, and it is considered not yet proven (experimental) by private insurance.

Codes:

1) **31242** Nasal/sinus endoscopy, surgical; with destruction by radiofrequency ablation, posterior nasal nerve
2) **31243** Nasal/sinus endoscopy, surgical; with destruction by cryoablation, posterior nasal nerve

Information: Information: Posterior nasal nerve ablation is a treatment for chronic rhinitis, which causes a runny nose or post-nasal drip. Other treatments for chronic rhinitis include intranasal saline, intranasal corticosteroids, intranasal anticholinergics, oral/topical antihistamines, and/or oral/topical decongestants. Posterior nasal nerve ablation is a minimally invasive procedure to disrupt this nerve and reduce parasympathetic innervation to the nasal cavity. Chronic rhinitis (ICD-10-CM J31.0) is on line 562.

Evidence

Balai 2023, systematic review and meta-analysis of posterior nasal nerve neurectomy for rhinitis

1. 6 single arm studies and 2 sham controlled RCTs (463 total patients)
    a. 6 of the 8 studies were industry sponsored
    b. 6 studies on cryotherapy, 1 study on radiofrequency ablation and 1 study on laser ablation
    c. 4 single arm studies considered to be at moderate risk of bias and 2 at serious risk of bias. The two randomized sham-controlled trials were both deemed to be at an overall low risk of bias
2. In the pre-post single-arm studies the primary outcome was a change in TNSS from pre-operative baseline, to varying intervals of post-operative follow-up. Whereas in the two randomized sham-controlled trials the primary outcome was responder rate at follow-up, where a response was defined as a ≥ 30% improvement (decrease) in TNSS from baseline. Timing of outcome measures ranged from 7 days to 2 years post-procedure.
3. In the pooled analysis of data from these two randomized controlled trials [Del Signore 2021--cryoablation, Stolovitzky 2021—radiofrequency ablation], active treatment was associated with significantly greater responder rate (OR 3.85, 95%CI 2.23-6.64, $p < 0.00001$).

4. Conclusion: This systematic review identified there is some limited evidence to suggest cryotherapy or radiofrequency ablation of the posterior nasal nerve can improve TNSS in adult patients. However, this is from a limited number of trials with short follow-up. Future research should focus on prospective randomized controlled trials with larger numbers of participants and medium to long term follow up in order to help draw more valid conclusions regarding the true effectiveness of PNNN in this patient cohort

Expert guidelines

American Academy of Otolaryngology-Head and Neck Surgery 2023, position statement: PNN ablation for the treatment of chronic rhinitis

1) Available at: https://www.entnet.org/resource/position-statement-posterior-nasal-nerve/
    a. Accessed October 5, 2023
2) Based on these safety and efficacy data, the AAO endorses the use of PNN ablation for the treatment of medically-refractory chronic rhinitis. We do not consider these treatments to be experimental

Other payer policies

1) Premara BCBS 2023
    a. Cryoablation for chronic rhinitis (allergic or nonallergic) is considered investigational. (e.g., Clarifix™device)
    b. Radiofrequency ablation for chronic rhinitis (allergic or nonallergic) is considered investigational. (e.g., RhinAer™ stylus)
2) Aenta 2023: considers nerve ablation for the treatment of rhinitis to be experimental

HERC staff summary

Ablation of the posterior nasal nerve (cryotherapy or radiofrequency ablation) has not been well studied. The existing studies are mostly cohort studies, the majority are industry sponsored, and all are short term. Private payers consider these procedures to be experimental.

HERC staff recommendations:

1) Place posterior nasal nerve ablation CPT codes on line 662
    1. **31242** Nasal/sinus endoscopy, surgical; with destruction by radiofrequency ablation, posterior nasal nerve
    2. **31243** Nasal/sinus endoscopy, surgical; with destruction by cryoablation, posterior nasal nerve
2) Add an entry to GN173 as shown below

2023 CPT Code Review
Posterior Nasal Nerve Ablation

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

Line 662

The following Interventions are prioritized on Line 662 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
31242, 31243	Nasal/sinus endoscopy, surgical; with destruction by radiofrequency ablation or cryoablation, posterior nasal nerve	Insufficient evidence of effectiveness	November 2023

Eur Ann Allergy Clin Immunol Vol 55, N.3, 101-114, 2023

Edward Balai[1], Keshav Kumar Gupta[2], Karan Jolly[2], Adnan Darr[3]

Posterior nasal nerve neurectomy for the treatment of rhinitis: a systematic review and meta-analysis

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Key words

Allergy; rhinology; chronic rhinitis; posterior nasal nerve; neurectomy.

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Impact statement

This systematic review shows there is some limited evidence to suggest posterior nasal nerve neurectomy can improve rhinitis symptoms in adult patients, and the incidence of serious adverse events associated with posterior nasal nerve ablation appears to be low.

Summary

Background. *Posterior nasal nerve neurectomy (PNNN) is a surgical option for the treatment of refractory chronic rhinitis. It can be performed by surgical dissection, cryotherapy, or laser ablation. This systematic review aimed to assess the effect of PNNN on Total Nasal Symptom Score (TNSS) in adults with chronic rhinitis.* ***Methods.*** *A systematic review of EMBASE, MEDLINE, PubMed and ClinicalKey databases was conducted in November 2021. Studies reporting PNNN performed as a single procedure in adult patients with allergic, non-allergic or mixed chronic rhinitis, and TNSS as the outcome measure, were included.* ***Results.*** *Database search identified 39 articles, of which 8 (463 patients) were included in the review. Two were randomized sham-controlled trials and six were prospective single-arm, unblinded and uncontrolled studies. Pooled analysis of data from the two randomized controlled trials found active treatment was associated with a significantly greater response ≥ (30% reduction in TNSS from baseline) rate (OR 3.85, 95%CI 2.23-6.64, $p < 0.00001$).* ***Conclusions.*** *This systematic review identified there is some limited evidence to suggest cryotherapy or radiofrequency ablation of the posterior nasal nerve can improve TNSS in adult patients. However, this is from a limited number of trials with short follow-up. Future research should focus on prospective randomized controlled trials with larger numbers of participants and medium to long term follow up in order to help draw more valid conclusions regarding the true effectiveness of PNNN in this patient cohort.* ***Study registration.*** *The systematic review was registered prospectively on the PROSPERO database in July 2021 (ID: CRD42021270486).*

Introduction

Rhinitis is chronic condition characterized by inflammation of the nasal mucosa, associated with symptoms of congestion, rhinorrhea, sneezing, pruritis that are present for at least 12 weeks per year. It has a global prevalence of 30% (1), affecting 10-20% of adults in the United Kingdom (UK) and United States of America (USA) (2, 3), and can lead to a significant reduction in quality of life and high health-care utilization. Whilst medical therapy remains the mainstay of management, approximately 10-22% of patients will be refractory to such intervention (4). Surgical options include inferior turbinate surgery in combination with vidian neurectomy (VN) or posterior nasal nerve neurectomy (PNNN), of which the latter two aim to eliminate the parasympathetic autonomic supply to the nasal mucosa (5). PNNN differs from VN by targeting only the post-ganglionic posterior nasal branches as they exit the sphenopalatine foramen. This modification is thought to be a safer technique with a lower incidence of complications such as cheek and palatal numbness, and dry eyes (6).

PNNN can be performed either by surgical dissection and nerve resection, cryotherapy, radiofrequency, and laser ablation. These

2023 CPT Code Review
Phrenic Nerve Stimulator

Plain Language Summary:

Coverage question: Should OHP cover a device that uses electrical pulse to make the nerve a in the neck work better to help a person who is using a breathing machine?

Should OHP cover this treatment? Yes. This is a standard option for treatment of certain patients who are very ill.

Codes:

1) **33276** Insertion of phrenic nerve stimulator system (pulse generator and stimulating lead[s]), including vessel catheterization, all imaging guidance, and pulse generator initial analysis with diagnostic mode activation, when performed
2) **33277** Insertion of phrenic nerve stimulator transvenous sensing lead
3) **33278** Removal of phrenic nerve stimulator, including vessel catheterization, all imaging guidance, and interrogation and programming, when performed; system, including pulse generator and lead(s)
4) **33279** Removal of phrenic nerve stimulator, including vessel catheterization, all imaging guidance, and interrogation and programming, when performed; transvenous stimulation or sensing lead(s) only
5) **33280** Removal of phrenic nerve stimulator, including vessel catheterization, all imaging guidance, and interrogation and programming, when performed; pulse generator only
6) **33281** Repositioning of phrenic nerve stimulator transvenous lead(s)
7) **33287** Removal and replacement of phrenic nerve stimulator, including vessel catheterization, all imaging guidance, and interrogation and programming, when performed; pulse generator
8) **33288** Removal and replacement of phrenic nerve stimulator, including vessel catheterization, all imaging guidance, and interrogation and programming, when performed; transvenous stimulation or sensing lead(s)
9) **93150** Therapy activation of implanted phrenic nerve stimulator system, including all interrogation and programming
10) **93151** Interrogation and programming (minimum one parameter) of implanted phrenic nerve stimulator system
11) **93152** Interrogation and programming of implanted phrenic nerve stimulator system during polysomnography
12) **93153** Interrogation without programming of implanted phrenic nerve stimulator system

Information: The phrenic nerve stimulator provides electrical stimulation of the patient's phrenic nerve. The phrenic nerve causes the diaphragm to contract and relax. A phrenic nerve stimulator causes the diaphragm to contract rhythmically and produce breathing in patients who have hypoventilation (a state

in which an abnormally low amount of air enters the lungs). The device is used to treat hypoventilation caused by a variety of conditions, including respiratory paralysis resulting from lesions of the brain stem and cervical spinal cord and chronic pulmonary disease with ventilatory insufficiency. The phrenic nerve stimulator is intended to be an alternative to management of patients with respiratory insufficiency who are dependent upon the usual therapy of intermittent or permanent use of a mechanical ventilato..

Similar codes:

1) Previously was coded with 64575 (Incision for implantation of neurostimulator electrode array; peripheral nerve) and similar codes. These codes are Ancillary

Current Prioritized List status

1) Quadriplegia is on the 4 dysfunction lines
2) Central hypoventilation syndrome is on line 202 SLEEP APNEA, NARCOLEPSY AND REM BEHAVIORAL DISORDER
3) Respiratory failure is on line 233 ADULT RESPIRATORY DISTRESS SYNDROME; ACUTE RESPIRATORY FAILURE; RESPIRATORY CONDITIONS DUE TO PHYSICAL AND CHEMICAL AGENTS

Expert guidelines

American Thoracic Society 2016

1. Diaphragm pacing is a way to help support people who cannot breathe on their own. It can be used in place of a mechanical ventilator at times. It is a treatment option for some people diagnosed with congenital central hypoventilation syndrome (CCHS) as well as those who have suffered a high cervical spinal cord injury.
2. To be a candidate, a patient must have normal diaphragm muscle function, intact phrenic nerves, mild or no lung disease
3. The main risks of diaphragm pacing include risk of injury to the phrenic nerve during surgery, infection of implanted components, and failure of the equipment

Other payer policies

1) CMS
    a. The implantation of a phrenic nerve stimulator is covered for selected patients with partial or complete respiratory insufficiency
2) Cigna 2023
    a. Covers phrenic nerve stimulation for patients with severe, chronic respiratory failure requiring mechanical ventilation for either of the following:
        i. stable, high spinal cord injury
        ii. hypoventilation, either primary or secondary to a brainstem disorder
    b. Considers phrenic nerve stimulation to be experimental for central sleep apnea, amyotrophic lateral sclerosis (AL), temporary respirator insufficiency
3) Wellmark BCBS 2023

   a. Covers phrenic nerve stimulation as an alternative to mechanical ventilation for patients with central hypoventilation syndrome or ventilatory failure from stable spinal cord injury at or above C3
   b. Experimental for central sleep apnea, motor neuron disease or when respiratory insufficiency is temporary
4) Aetna 2023
   a. Covers phrenic nerve pacing for members with high quadriplegia at or above C3 or central hypoventilation, patients with ALS meeting certain criteria, or moderate to severe central sleep apnea

HERC staff summary

Phrenic nerve stimulation appears to be a standard option for treatment of central hypoventilation syndrome and high spinal cord injury, to allow patients to have a break from mechanical ventilation. Its use requires an intact phrenic nerve and diaphragm. Use of this technology for patients with motor neuron disease such as ALS, severe obstructive sleep apnea, or temporary mechanical ventilation appears to be an area of research. This technology was previously covered with generic nerve stimulation codes, which are Ancillary. HERC staff recommends adding this technology to the dysfunction in breathing line with consideration of adding a new guideline.

HERC staff recommendations:

1) Place the various codes for phrenic nerve pacing on line 71 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES
   1. **33276** Insertion of phrenic nerve stimulator system (pulse generator and stimulating lead[s]), including vessel catheterization, all imaging guidance, and pulse generator initial analysis with diagnostic mode activation, when performed
   2. **33277** Insertion of phrenic nerve stimulator transvenous sensing lead
   3. **33278** Removal of phrenic nerve stimulator, including vessel catheterization, all imaging guidance, and interrogation and programming, when performed; system, including pulse generator and lead(s)
   4. **33279** Removal of phrenic nerve stimulator, including vessel catheterization, all imaging guidance, and interrogation and programming, when performed; transvenous stimulation or sensing lead(s) only
   5. **33280** Removal of phrenic nerve stimulator, including vessel catheterization, all imaging guidance, and interrogation and programming, when performed; pulse generator only
   6. **33281** Repositioning of phrenic nerve stimulator transvenous lead(s)
   7. **33287** Removal and replacement of phrenic nerve stimulator, including vessel catheterization, all imaging guidance, and interrogation and programming, when performed; pulse generator

8. **33288** Removal and replacement of phrenic nerve stimulator, including vessel catheterization, all imaging guidance, and interrogation and programming, when performed; transvenous stimulation or sensing lead(s)
9. **93150** Therapy activation of implanted phrenic nerve stimulator system, including all interrogation and programming
10. **93151** Interrogation and programming (minimum one parameter) of implanted phrenic nerve stimulator system
11. **93152** Interrogation and programming of implanted phrenic nerve stimulator system during polysomnography
12. **93153** Interrogation without programming of implanted phrenic nerve stimulator system

2) Add the following HCPCS codes to line 71
    1. C1778 Lead, neurostimulator (implantable)
    2. C1816 Receiver and/or transmitter, neurostimulator (implantable)
    3. L8680 Implantable neurostimulator electrode, each
    4. L8682 Implantable neurostimulator radiofrequency receiver
    5. L8683 Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
3) Consider adding a new guideline to line 71 as shown below

GUIDLEINE NOTE XXX PHRENIC NERVE STIMULATION

Line 71

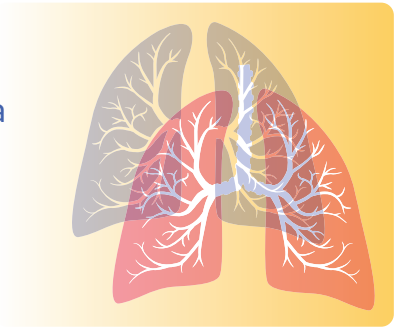
Phrenic nerve stimulation is included on this line when all of the following criteria are met

1) The patient has severe, chronic respiratory failure requiring mechanical ventilation due to EITHER
    a. A stable high spinal cord injury; OR
    b. Central alveolar hypoventilation disorder; AND
2) The patient has intact and sufficient function in the phrenic nerve, lungs, and diaphragm; AND
3) Stimulation of the diaphragm either directly or through the phrenic nerve results in sufficient muscle activity to accommodate independent breathing without the support of a ventilator for at least 4 continuous hours and day.

Diaphragm Pacing by Phrenic Nerve Stimulation

What is diaphragm pacing?

Diaphragm pacing is a way to help support people who cannot breathe on their own. It can be used in place of a mechanical ventilator at times. It is a treatment option for some people diagnosed with congenital central hypoventilation syndrome (CCHS) as well as those who have suffered a high cervical spinal cord injury.



The diaphragms are large muscles found under each lung that are the major muscles used in breathing. The phrenic nerves send a signal to the diaphragms stimulating them to breathe. People who have problems with the brain or spinal cord at times do not send the signals well to breathe. Diaphragm pacing can use the phrenic nerves to send the signals to a person's diaphragm muscles to contract and take a breath in. Often management of diaphragm pacers is done by special medical care centers, some of whom have had experience with this for decades.

How does it work?

Diaphragm pacing uses the person's own diaphragms as the "ventilator." A diaphragm pacer system involves 4 components:

- electrodes that are surgically attached to the phrenic nerves on each side of the neck or in the chest,
- receivers that are surgically implanted in the abdomen or chest,
- antennae which are taped on the chest over the receivers during pacing,
- portable external transmitter machine.

When turned on, the transmitter sends a signal to the receivers through the antennae. The external transmitter generates electrical energy similar to radio wave signals. The receiver converts this energy signal to electrical current that is conducted to the phrenic nerves. The nerve stimulation causes the diaphragm muscles to contract and the person takes a breath in. This cycle repeats for the number of breaths needed each minute. A respiratory rate is set for the transmitter for how often to trigger a breath.

What are the advantages of diaphragm pacing?

Diaphragm pacing is an attractive treatment option for two reasons. First, it allows for the possibility of removal of the tracheostomy in people who require mechanical ventilator support only during sleep. Second, for people who need support full time (both day and night), it permits some freedom from the ventilator that may allow easier speech or participation in certain types of activities.

Who is a candidate for diaphragm pacing?

For a person to be considered for diaphragm pacing, one must be sure that:

- there is normal diaphragm muscle function,
- the phrenic nerves are intact and able to send a signal when stimulated,
- The person has relatively mild or no lung disease. This system does not work well if the lungs don't work well.

Testing can be done to check whether the phrenic nerves and diaphragms work normally. A lung specialist will evaluate the person to see how healthy his or her lungs are and whether this is an option to consider. People who are very obese may not be good candidates for pacing. There may be too much fat tissue between the antenna and receiver that can limit getting a good signal to the phrenic nerves. With obesity, it may not be possible to find a consistent diaphragm pacer setting to achieve adequate ventilation.

What happens during surgery?

Surgery is done with general anesthesia so a person is asleep for the whole procedure. This surgery is delicate and usually is performed in specialized centers experienced with diaphragm pacing. Both the phrenic

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nerve electrodes and diaphragm pacer receivers are put in place. Usually these are placed on both the right and left side with small incisions (thoracoscopic surgery). Phrenic nerve electrodes are attached to the nerves in the upper chest/neck area or lower in the chest. The phrenic nerve electrodes are connected inside by lead wires to the receivers, which are implanted on each side just under the skin, either on the upper abdomen or in the upper chest. The diaphragm pacer equipment is tested during the surgery to be sure that it is functional.

When is diaphragm pacing started?

Diaphragm pacing is not used right after surgery. It is best to wait for the incisions to heal, and for scar tissue formation around the nerve electrodes to stabilize them. Diaphragm pacing is generally started about 6-8 weeks after surgery. Most of the time, it is first turned on with observation in the hospital. Often, pacing can only be done for 1-1.5 hours per night at first before the diaphragms get tired (fatigue). The time on pacers is gradually increased. This gradual process is necessary even in people who breathe on their own while awake.

It is thought that the diaphragm signals that the phrenic nerves send with the pacer is different from the natural phrenic nerve impulses. This takes some getting used to. So, it is necessary to train the diaphragm to accept longer periods of pacing without fatigue. The time pacing is gradually increased and usually, patients are pacing up to 8-12 hours at a time by about 3 months. This is the usual maximum time pacers are used. Twenty- four hour diaphragm pacing is not recommended because of diaphragm fatigue. Therefore, for people who depend on full time assisted ventilation, there is a need to have another method of ventilatory support such as home mechanical ventilation by tracheostomy or noninvasive positive pressure ventilation for use when not pacing. Your specialist can help you decide how much time you could use pacers and whether they are the right choice to help support your breathing.

People using diaphragm pacers should have a pulse oximeter to check their oxygen saturation levels (see ATS Patient Information Series "Pulse Oximetry"). Ideally, one should also have a machine to measure the carbon dioxide (CO_2) level, which is what we breathe out to rid the body of extra acid. This can be done using an exhaled CO_2 monitor. This equipment requires prescription and insurance approvals that will need to be done when planning for pacer placement.

What are the risks of diaphragm pacing?

Diaphragm pacing is generally very well tolerated. The main risks of diaphragm pacing include risk of injury to the phrenic nerve during surgery, infection of implanted components, and failure of the equipment. Changing body positions, which can compress or increase the distance between the antenna and receiver, can result in decreased or increased diaphragm contractions. It is important to get the right settings for the position that the person will use the pacers. If a person has a respiratory infection, the settings may need to be adjusted during the illness or at times another form of ventilator support used.

Obstructive sleep apnea may occur in those who are diaphragm pacing without tracheostomy. Because a diaphragm pacer breath is generated by direct stimulation of the phrenic nerve, there is no synchronous contraction of upper airway skeletal muscles with each inspiration. This can result in upper airway collapse and obstructive apnea. Usually, this can be improved by adjusting the diaphragm pacer setting.

Authors: Iris A. Perez, MD, Sheila Kun, RN, MSN, Thomas G. Keens, MD
Reviewer: Marianna Sockrider, MD, DrPH

Adapted from the ATS Clinical Statement on Congenital Central Hypoventilation Syndrome. http://www.thoracic.org/newsroom/press-releases/resources/cchs-statement.pdf

Rx Action Steps

- ✔ Talk to your lung specialist to see if you are a candidate for diaphragm pacing.
- ✔ Discuss if tests need to be done to check on your phrenic nerve and diaphragm function.
- ✔ Ask to be referred to a center specializing in diaphragm pacing if you are a possible candidate.

Healthcare Provider's Contact Number:

_____

Other Resources:

Introduction to Diaphragmatic Pacing—Children's Hospital of Los Angeles
https://www.youtube.com/watch?v=ZbhPbcd4yrI

Diaphragmatic Pacing- Trouble shooting Tips—Children's Hospital of Los Angeles
https://www.youtube.com/watch?v=gI174Yv2yUs

ATS Patient Information Series
www.thoracic.org/patients

- Congenital Central Hypoventilation Syndrome (CCHS)
- Mechanical Ventilation
- Pulse Oximetry

2023 CPT Code Review
Urethral Stricture Dilation with Drug-Coated Balloon Catheter

Plain Language Summary:

Coverage question: Should a procedure that uses a tube coated with medicine to open the urethra be covered?

Should OHP cover this treatment? No, this procedure is not well studied.

Code: **52284** Cystourethroscopy, with mechanical urethral dilation and urethral therapeutic drug delivery by drug-coated balloon catheter for urethral stricture or stenosis, male, including fluoroscopy, when performed

Information: Urethral strictures are scar tissue that narrows the urethral and can cause lower urinary tract symptoms such as urinary retention. Current available options for recurrent urethral strictures include endoscopic management and urethral reconstruction. While open repair is considered the gold standard, with success rates of 80–95%, minimally invasive therapies are more frequently used. The Optilume® Drug Coated Balloon (DCB) (Urotronic, Inc., Plymouth, MN, USA) is the first drug coated balloon catheter intended for the treatment of male anterior urethral strictures. This technology aims to provide immediate symptomatic relief by widening the urethral lumen using balloon dilation, while maintaining long-term urethral patency via the circumferential and local application of paclitaxel. Paclitaxel is an antimitotic agent that inhibits cell proliferation and migration.

Evidence

Elliot 2022, one year results of the ROBUST III RCT

1) RCT of drug-coated balloon dilation (DCB) vs direct vision internal urethrotomy (DVIU)
2) N=127 patients enrolled (N=79 DCB vs N=48 DVIU)
    a. 100 patients evaluated at 6 months (N=69 DCB group, N=31 DVIU group)
    b. 75 patients evaluated at 1 year (N=60 DCB group, N=15 DVIU group)
    c. Anterior strictures ≤ 12 Fr in diameter and ≤ 3 cm in length with at least 2 prior endoscopic treatments, International Prostate Symptom Score ≥ 11 and maximum flow rate < 15 ml second
    d. Participants with previous urethroplasty, hypospadias repair, lichen sclerosis or unresolved confounding etiologies (eg bladder neck contracture, neurogenic bladder, benign prostatic hyperplasia) were excluded.
    e. Primary endpoint was anatomical success s (≥ 14Fr by cystoscopy or calibration) at 6 months
    f. Secondary end points included freedom from repeat treatment, International Prostatic Symptom Score and peak flow rate
3) At 6 months, anatomical success was 74.6% in the DCB group and 26.8% in the control group

4) Kaplan-Meier estimates of freedom from repeat intervention through 1 year were significantly higher for the DCB group as compared to the control group (83.2% vs 21.7%, p <0.0001)
5) QOL scores for the DCB group remained significantly improved through 1 year, while the DVIU group had deterioration of QOL scores
6) Adverse event types and rates were well matched between groups, except that the DCB group had higher rates of post-procedure hematuria and dysuria compared to controls (11.4% vs 2.1% for both event types).
7) Conclusion: The results of this randomized controlled trial support that Optilume DCB is safe and superior to standard DVIU/dilation for the treatment of recurrent anterior urethral strictures
8) Limitation: DCB was not compared to urethroplasty, the gold standard urethral stricture treatment. Urethroplasty has anatomical success rates of 80%-95% depending on stricture characteristics. However, urethroplasty is more invasive than endoscopic treatment and can be associated with complications of pain, neuropathy and sexual dysfunction.
9) HERC staff evaluation: this is a small trial, with a high drop out rate in the control arm (68.75% drop out rate in the control arm vs 24.05% in the DCB arm). This large mismatch in drop out rates makes the results of this study less reliable. Additionally, this study only included patients who had multiple previous endoscopic dilations, which gives no information on how DCB performs when done as for first time treatment of strictures.

DeLong 2022, 1 year results of the ROBUST II study

1) Cohort study of patients with a single anterior urethral stricture ≤ 3 cm in length and at least 2 prior stricture treatments.
2) N=16 patients enrolled, N=9 completed 1 year follow up
3) The primary safety endpoint was the rate of treatment-related serious complications at 90 days post-procedure. Efficacy outcomes included symptomatic assessments, erectile function measured using the International Index of Erectile Function (IIEF), Qmax, and anatomic success
4) The anatomic success rate at 6 months was 73.3% (11/15). The average IPSS decreased from 18.4 at baseline to 7.5 at 90 days, 7.0 at 6 months, and 6.0 at 1 year (P < 0.001). The IPSS responder rate was 75.0% (12/16) at 30 days and 61.5% (8/13) at 1 year. The average PROM score also improved after the procedure, decreasing from 10.8 at baseline to 3.6 at 90 days, 4.2 at 6 months, and 4.3 at 1 year (P < 0.001). Quality of life as measured by IPSS QOL improved from 4.4 at baseline to 1.4 at 1 year (P < 0.001).
5) Results of the ROBUST II study showed that treatment of recurrent anterior urethral stricture with the minimally invasive Optilume DCB was safe and achieved durable anatomic results at 6 months, with sustained reduction in severity of LUTS through 1 year

Virasoro 2022: 3 year results from the ROBUST I study

1. Single arm open-label study, N=53 patients enrolled, N=33 patients actually followed for 3 years
    a. Adult men with a single bulbar stricture <12F and ≤ 2 cm long
    b. Protocol exclusions included prior urethroplasty, radical prostatectomy, lichen sclerosus, penile prosthesis or artificial urinary sphincter, and history of pelvic radiation
2. At 3 years, 67% (29/43) of subjects achieved functional success based on an improvement in IPSS ≥50% without retreatment

3. The average International Prostate Symptom Score (IPSS) improved from 25.2 at baseline to 5.5 at 3 years ($p<0.0001$)
4. Freedom from repeat intervention was 77% (33/43) at 3 years
5. A total of 73 adverse events in 35 subjects were reported through 3 years
6. Symptomatic improvement after treatment with the Optilume DCB was maintained through 3 years in a population susceptible to high stricture recurrence rate. The therapy is safe with no negative impact on sexual function

Kaplan 2021, interim 2 year results for the EVEREST-I trial evaluating the Optilume BHP catheter system

1) Only available as a poster abstract

Expert guidelines

American Urologic Association 2023, Urethral stricture disease

1. Surgeons may offer urethral dilation or direct visual internal urethrotomy, combined with drug-coated balloons, for recurrent bulbar urethral strictures <3cm in length. (Conditional Recommendation; Evidence Level: Grade B)
2. Drug coated balloons have not been assessed in RCTs for first-time treatment of anterior urethral stricture.
3. Only trial noted to be the ROBUST trial
4. The Panel suggests the following issues in future investigations: The efficacy of injection or balloon-coated antiproliferative or other pharmacological agents at time of endoscopic treatment for penile urethral stricture, previous failed urethroplasty, posterior urethral stenosis, and bladder neck contracture.

Other payer policies

1) Aetna 2023
    a. Drug-coated balloons (e.g., the Optilume paclitaxel-coated balloon) is considered investigational.
2) Cigna 2023
    a. Transurethral balloon dilation of the prostatic urethra is considered investigational
3) Wellmark BCBS 2023
    a. Drug Coated Balloon (Optilume): Based on the current peer reviewed medical literature 1-year outcomes from the EVEREST-I study may show promise, however, study limitations include the lack of a control group, and a randomized clinical trial is currently ongoing to confirm the findings. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.
    b. Considers Optilume to be experimental

Expert input

Dr. Jyoti Chouhan, OHSU urology

Optilume (the drug coated urethral balloon that is noted in the prior e-mail) was FDA approved last year for the management of recurrent bulbar urethral strictures < 3 cm. In my opinion, it is

not experimental. Our national organization (the American Urological Association) updated the urethral stricture guidelines earlier this year due to the FDA approval of Optilume (and the studies behind it) and their recommendation is noted below [cites AUA 2023 guideline as above]

While I agree that this is a conditional recommendation, there are many parts of the guideline that are also conditional recommendations and refer to techniques that have been around for decades and are far from experimental (traditional urethral dilation, direct visualized internal urethrotomy, urethroplasty).

Male reconstruction studies are frought w/ suboptimal study designs- usually small, retrospective cohorts. Therefore, the recommendations in guidelines (such as the one above) are often Grade B or C (and not A). This is to be expected in this field.

HERC staff summary

Treatment of urethral strictures with a drug-eluting balloon dilation has been studied in three small cohort studies and one small RCT. The only RCT available (ROBUST III) compares drug eluting balloon dilation to endoscopic dilation, not the standard of care which is urethroplasty. The RCT also had a much higher drop out rate in the control group, making comparisons difficult. Additionally ROBUST III included only patients with multiple prior stricture dilations. There is no RCT comparing drug eluting balloon dilation to standard therapy (either minimally invasive or open) for first time dilation. The AUA has a conditional recommendation for use with a note that future investigations should be conducted. Oregon experts recommend covering this therapy as a minimally invasive treatment option for urethral stricture. Other treatments for urethral strictures are currently included on the Prioritized List. Private payers surveyed consider this intervention to be experimental.

HERC staff recommendations:

1) Place CPT **52284 (**Cystourethroscopy, with mechanical urethral dilation and urethral therapeutic drug delivery by drug-coated balloon catheter for urethral stricture or stenosis, male, including fluoroscopy, when performed) on line 662
2) Add an entry to GN173 as shown below
3) Readdress when and RCT is published comparing drug-eluting balloon dilation with other therapies or sham procedures

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

Line 662

The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

2023 CPT Code Review
Urethral Stricture Dilation with Drug-Coated Balloon Catheter

Procedure Code	Intervention Description	Rationale	Last Review
52284	Cystourethroscopy, with mechanical urethral dilation and urethral therapeutic drug delivery by drug-coated balloon catheter for urethral stricture or stenosis	Insufficient evidence of effectiveness	November 2023

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JU Insight

OPEN

One-Year Results for the ROBUST III Randomized Controlled Trial Evaluating the Optilume® Drug-Coated Balloon for Anterior Urethral Strictures

Sean P. Elliott, Karl Coutinho, Kaiser J. Robertson et al.

Correspondence: Sean P. Elliott (email: selliott@umn.edu).

Full-length article available at www.auajournals.org/10.1097/JU.0000000000002346.

Study Need and Importance: The gold standard treatment of urethral stricture is urethroplasty with 90% success, but the most common treatments by far are urethral dilation and/or direct vision internal urethrotomy (DVIU). Dilation/DVIU is successful in <50%, especially in recurrent disease. This creates a need for a therapy that is less invasive than urethroplasty but more successful than dilation/DVIU. The Optilume® paclitaxel-coated balloon combines urethral dilation with circumferential delivery of an antiproliferative agent that inhibits fibroblast growth and stricture recurrence.

What We Found: We randomized 127 men to Optilume vs dilation/DVIU. At 6 months, the rate of anatomic success (defined by the ability to pass a flexible cystoscope) was 75% for Optilume and 27% for dilation/DVIU. Several different 1-year outcomes were also superior for Optilume vs dilation/DVIU: freedom from repeat intervention was 83% vs 22% (see figure), urinary symptoms as measured by the International Prostate Symptom Score were 9 vs 20 and maximum urinary flow rate was 16 vs 8 ml per second, respectively. Most side effects were similar across treatments except hematuria and dysuria, which were more common after Optilume (11% vs 2% for both events).

Limitations: As this trial only compared Optilume with dilation/DVIU, we don't know how Optilume would compare with urethroplasty. It is possible that the early positive results are impacted by surgeons opening the urethra to a larger size with Optilume; however, immediately post-treatment the luminal diameter, measured by urethrogram, was the same (8 mm) in both groups.

Interpretation for Patient Care: Early findings indicate that Optilume offers superior outcomes to dilation/DVIU for men with recurrent bulbar urethral stricture. Men who have suffered stricture recurrence after dilation/DVIU may consider Optilume as an alternative to repeat dilation/DVIU.

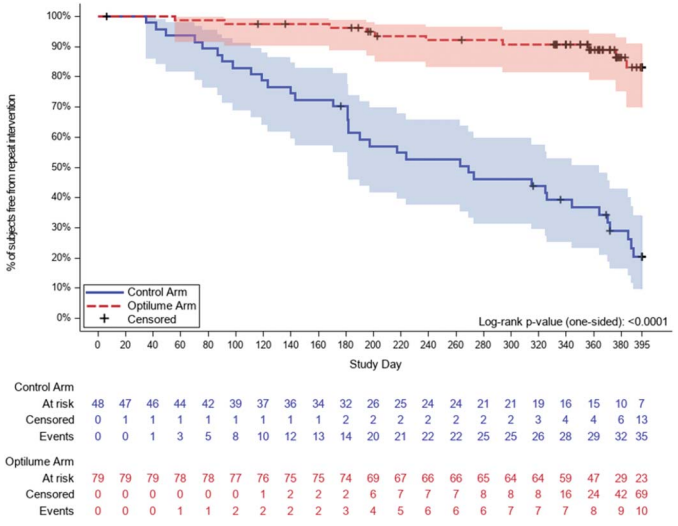

Figure. Kaplan-Meier curve of freedom from reintervention through 1 year.

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One-Year Outcomes of the ROBUST II Study Evaluating the Use of a Drug-Coated Balloon for Treatment of Urethral Stricture

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Abstract

Objectives To report 1-year results of the ROBUST II study investigating the safety and efficacy of a paclitaxel-coated balloon for the treatment of recurrent urethral strictures.

Methods Subjects were adult men with a single anterior urethral stricture ≤ 3 cm in length and at least 2 prior stricture treatments. After treatment with the Optilume urethral drug-coated balloon (DCB), subjects were followed through 1 year. The primary safety endpoint was the rate of treatment-related serious complications at 90 days post-procedure. Efficacy outcomes included symptomatic assessments, erectile function measured using the International Index of Erectile Function (IIEF), Qmax, and anatomic success.

Results Sixteen men with an average of 4.1 prior dilations were treated with the DCB. Anatomic success was achieved at 6 months in 73%. Average IPSS improved from 18.4 to 6.0 at 1 year ($P < 0.001$). Qmax improved from 6.9 mL/sec to 20.8 mL/sec ($P < 0.001$). There was no change in IIEF. Four subjects received additional treatment within 1 year. There were no treatment-related serious complications.

Conclusions Short-term follow-up of men with urethral stricture treated with the Optilume DCB showed durable anatomic results at 6 months and sustained symptomatic improvement through 1 year. Treatment with the device was safe.

Introduction

Urethral stricture disease occurs in approximately 0.6% of men[1]. Formation of scar tissue leads to narrowing of the urethral lumen resulting in obstructive lower urinary tract symptoms (LUTS) and associated morbidities that negatively impact patient quality of life[1]. Several treatment options are available for stricture, including rigid rod or balloon dilation, direct visual urethrotomy (DVIU), and urethroplasty[2]. Although dilation and DVIU are widely used for stricture treatment, durability is poor, with long-term stricture-free rates estimated between 8% and 30% after a single treatment[3–5]. Furthermore, multiple treatments of the same stricture lead to progressively worse outcomes, with success rates approaching 0% at 2 years after a third treatment. Urethroplasty is recommended for patients with recurrent strictures or strictures > 2 cm long and has reported success rates > 80% depending on approach and stricture characteristics[6].

Key Words

Urethral stricture, dilatation, drug-coated balloon, paclitaxel, lower urinary tract symptoms

Competing Interests

The study was sponsored and funded by Urotronic Inc.

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CLINICAL TRIAL REPORT

A Drug-Coated Balloon Treatment for Urethral Stricture Disease: Three-Year Results from the ROBUST I Study

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Introduction: Endoscopic management of male anterior urethral stricture disease is common; however, repeat treatment is associated with high recurrence rates. Here, we report the 3-year results of the ROBUST I trial, which evaluated the safety and efficacy of the Optilume® drug coated balloon (DCB) in men with recurrent urethral strictures.

Methods: Adult men with recurrent bulbar urethral strictures ≤2 cm in length and 1–4 prior endoscopic interventions were treated with the Optilume DCB. Functional success was defined as ≥50% reduction in International Prostate Symptom Score (IPSS) without need for retreatment. Other outcomes included quality of life, maximum flow rate, post-void residual urine volume, erectile function, and freedom from repeat intervention.

Results: Of the 53 enrolled and treated men, 33 completed the 3-year visit, with 10 patients experiencing clinical failures at previous visits, giving a total of 43 subjects evaluable for the functional success endpoint. Functional success was achieved in 67% (29/43) and freedom from retreatment in 77% (33/43). Average IPSS improved from 25.2 at baseline to 5.5 at 3 years ($p<0.0001$). Significant improvements were observed in quality of life, flow rate, and post-void residual urine volume. Erectile function was not affected by treatment. Device-related adverse events were mild or moderate in nature and resolved quickly after onset. There were no serious treatment-related adverse events.

Conclusion: Symptomatic improvement after treatment with the Optilume DCB was maintained through 3 years in a population highly susceptible to recurrent urethral stricture disease. This minimally invasive therapy is safe with no negative impact on sexual function.

Keywords: lower urinary tract symptoms, paclitaxel, urethral dilation, medical device, clinical trial

Introduction

The treatment of recurrent male anterior urethral stricture disease remains a common and challenging problem for many urologists across the globe. Current available options for recurrent urethral strictures include endoscopic management and urethral reconstruction. While open repair is considered the gold standard, with success rates of 80–95%, minimally invasive therapies are still more frequently used.[1] Of the primary endoscopic procedures, urethral dilation and Direct Vision Internal Urethrotomy (DVIU) have similar efficacy, with progressively lower probability of long-term success in repeat treatments.[2,3] More recently, small studies have evaluated targeted injections of antifibrotic agents as an adjunctive therapy to endoscopic procedures in an attempt to prevent or attenuate scar tissue formation.[4] The Optilume® Drug Coated Balloon (DCB) (Urotronic, Inc., Plymouth, MN, USA) is the first DCB intended for the treatment of male anterior urethral strictures. This technology aims to provide immediate symptomatic relief by widening the urethral lumen using balloon dilation, while maintaining long-term urethral patency via the circumferential and local application

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Authors' disclosure of potential conflicts of interest and author/staff contributions appear at the end of the article.

URETHRAL STRICTURE DISEASE: AUA GUIDELINE

(Published 2016; Amended 2023)

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Amendment: Hunter Wessells, MD; Allen Morey, MD; Lesley Souter, PhD; Alex Vanni, MD

SUMMARY

Purpose

The clinical guideline on urethral stricture provides a clinical framework for the diagnosis of urethral stricture and includes discussion of initial management, urethroplasty, reconstruction, contracture, stenosis, special circumstances, and post-operative follow-up care.

Methodology

A systematic review of the literature using the Pubmed, Embase, and Cochrane databases (search dates 1/1/1990 to 12/1/2015) was conducted to identify peer-reviewed publications relevant to the diagnosis and treatment of urethral stricture in men. The review yielded an evidence base of 250 articles after application of inclusion/exclusion criteria. The search for the 2023 Amendment used the Ovid, MEDLINE, Embase, and ClinicalTrials.gov databases and was modified to included females and males (search dates 12/2015 – 10/2022 for males; 01/1990 – 10/2022 for females) and one new Key Question on sexual dysfunction outcomes in men with bulbar urethral strictures was added (search dates: 01/1990 – 10/2022). All searches yielded 11,752 citations; after inclusion and exclusion criteria were applied, 81 studies were added to the existing evidence base. These publications were used to create the guideline statements. If sufficient evidence existed, then the body of evidence for a particular treatment was assigned a rating of A (high quality evidence; high certainty), B (moderate quality evidence; moderate certainty), or C (low quality evidence; low certainty) and evidence-based statements of Strong, Moderate, or Conditional Recommendation based on risks and benefits were developed. Additional information is provided as Clinical Principles and Expert Opinions when insufficient evidence existed.

GUIDELINE STATEMENTS

DIAGNOSIS/INITIAL MANAGEMENT

1. Clinicians should include urethral stricture in the differential diagnosis of patients who present with decreased urinary stream, incomplete emptying, dysuria, urinary tract infection, and after rising post-void residual. (*Moderate Recommendation; Evidence Level: Grade C*)

2. After performing a history, physical examination, and urinalysis, clinicians may use a combination of patient reported measures, uroflowmetry, and ultrasound post-void residual assessment in the initial evaluation of suspected urethral stricture. (*Clinical Principle*)
3. Clinicians should use urethro-cystoscopy, retrograde urethrography, voiding cystourethrography, or ultrasound urethrography to make a diagnosis of urethral stricture. (*Moderate Recommendation; Evidence Level: Grade C*)
4. Clinicians planning non-urgent intervention for a known stricture should determine the length and location of the urethral stricture. (*Expert Opinion*)
5. Surgeons may utilize urethral endoscopic management (e.g., urethral dilation, direct visual internal urethrotomy) or immediate suprapubic cystostomy for urgent management of urethral stricture, such as discovery of symptomatic urinary retention or need for catheterization prior to another surgical procedure. (*Expert Opinion*)
6. Surgeons may place a suprapubic cystostomy to promote “urethral rest” prior to definitive urethroplasty in patients dependent on an indwelling urethral catheter or intermittent self-dilation. (*Conditional Recommendation; Evidence Level: Grade C*)

DILATION/INTERNAL URETHROTOMY/URETHROPLASTY

7. Surgeons may offer urethral dilation, direct visual internal urethrotomy, or urethroplasty for the initial treatment of a short (<2cm) bulbar urethral stricture. (*Conditional Recommendation; Evidence Level: Grade C*)
8. Surgeons may perform either dilation or direct visual internal urethrotomy when performing endoscopic treatment of a urethral stricture. (*Conditional Recommendation; Evidence Level: Grade C*)
9. Surgeons may safely remove the urethral catheter within 72 hours following uncomplicated dilation or direct visual internal urethrotomy. (*Conditional Recommendation; Evidence Level: Grade C*)
10. In patients who are not candidates for urethroplasty, clinicians may recommend self-catheterization after direct visual internal urethrotomy to maintain urethral patency. (*Conditional Recommendation; Evidence Level: Grade C*)

11 a. Surgeons should offer urethroplasty, instead of repeated endoscopic management for recurrent anterior urethral strictures following failed dilation or direct visual internal urethrotomy. (*Moderate Recommendation; Evidence Level: Grade C*)

11 b. Surgeons may offer urethral dilation or direct visual internal urethrotomy, combined with drug-coated balloons, for recurrent bulbar urethral strictures <3cm in length. (*Conditional Recommendation; Evidence Level: Grade B*)

12. Surgeons who do not perform urethroplasty should refer patients to surgeons with expertise. (*Expert Opinion*)

ANTERIOR URETHRAL RECONSTRUCTION

13. Surgeons may initially treat meatal or fossa navicularis strictures with either dilation or meatotomy. (*Clinical Principle*)
14. Surgeons should offer urethroplasty to patients with recurrent meatal or fossa navicularis strictures. (*Moderate Recommendation; Evidence Level: Grade C*)
15. Surgeons should offer urethroplasty to patients with penile urethral strictures given the expected high recurrence rates with endoscopic treatments. (*Moderate Recommendation; Evidence Level: Grade C*)
16. Surgeons should offer urethroplasty as the initial treatment for patients with long (≥2cm) bulbar urethral stricturesgiven the low success rate of direct visual internal urethrotomy or dilation. (*Moderate Recommendation; Evidence Level: Grade C*)

2023 CPT Code Review
Transcervical Ablation of Uterine Fibroids

Plain Language Summary:

Coverage question: Should OHP cover a medical procedure to destroy noncancer growths in the uterus?

Should OHP cover this treatment? No, evidence does not support this specific medical procedure.

Code: **58580** Transcervical ablation of uterine fibroid(s), including intraoperative ultrasound guidance and monitoring, radiofrequency

Information: Uterine fibroids are non-cancerous growths in the uterus. Fibroids can cause symptoms such as heavy bleeding, pain, or pelvic fullness. Transcervical ablation of uterine fibroids is a minimally invasive treatment which involves insertion of a device through the cervix into the uterus which causes coagulative necrosis in the fibroid(s). Alternative treatments of fibroids include oral contraceptives, Mirena IUD, hysterectomy, myomectomy, endometrial ablation, and uterine artery embolization. Currently, vascular embolization, myomectomy, and hysterectomy are included on line 404 UTERINE LEIOMYOMA AND POLYPS for treatment of uterine fibroids, with a guideline. Transcervical radiofrequency ablation of fibroids was reviewed in 2021 and found to be experimental.

Previous HERC reviews:
The 2021 review of transcervical RFA for fibroids included a NICE 2021 evidence review, an AHRQ 2017 evidence review, and a 2019 systematic review and meta-analysis of prospective studies (Bradley 2019), as well as the 2021 ACOG practice bulletin on management of symptomatic uterine fibroids. Private payers were covering this technology in 2021. That review concluded that "Transcervical radiofrequency ablation has a small evidence base and has been found by one of our highly trusted sources (NICE) to have insufficient evidence of effectiveness."

Similar codes:
58674 (Laparoscopy, surgical, ablation of uterine fibroid(s) including intraoperative ultrasound guidance and monitoring, radiofrequency) is on line 404 UTERINE LEIOMYOMA
0404T (Transcervical uterine fibroid(s) ablation with ultrasound guidance, radiofrequency) is on line 662/GN173

Evidence
An updated evidence search was conducted, which found no additional studies, systematic reviews, or practice bulletins since the 2021 review

2023 CPT Code Review
Transcervical Ablation of Uterine Fibroids

Expert guidelines

ACOG 2021 Management of Symptomatic Uterine Leiomyomas

1) The only two minimally invasive interventions for leiomyomas that are recommended by ACOG are uterine artery embolization and laparoscopic radiofrequency ablation. Focused ultrasound and endometrial ablation both had insufficient evidence to make a clinical recommendation

Other payer policies

Private payers are covering this procedure for symptomatic fibroids as noted in the 2021 review

HERC staff summary

Transcervical ablation of uterine fibroids has no additional evidence or expert guideline recommendations to support its use since the 2021 HERC review. ACOG continues to not recommend this procedure. HERC staff recommend continuing non-coverage of this technology.

HERC staff recommendations:

1) Place **58580** (Transcervical ablation of uterine fibroid(s), including intraoperative ultrasound guidance and monitoring, radiofrequency) on line 662
2) Modify the entry to GN173 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 662

The following Interventions are prioritized on Line 662 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
~~0404T~~ 58580	~~Transcervical uterine fibroid(s) ablation with ultrasound guidance, radiofrequency~~ Transcervical ablation of uterine fibroid(s)	Insufficient evidence of effectiveness	~~August 2021~~ November 2023

MS NO: ONG-21-661

ACOG
The American College of Obstetricians and Gynecologists

ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 228

(Replaces Practice Bulletin Number 96, August 2008)

Committee on Practice Bulletins—Gynecology. This Practice Bulletin was developed by the ACOG Committee on Practice Bulletins–Gynecology in collaboration with Elizabeth A. Stewart, MD; Marisa R. Adelman, MD; and Vanessa L. Jacoby, MD, MAS.

Management of Symptomatic Uterine Leiomyomas

Uterine leiomyomas (fibroids) are the most common solid and symptomatic neoplasm in women. They are the leading indication for hysterectomy (1, 2), which is a definitive and effective surgical treatment for leiomyoma. However, many patients benefit from and seek out management options other than hysterectomy because they desire future childbearing or wish to retain their uterus. The purpose of this Practice Bulletin is to provide updated evidence-based recommendations for the medical, procedural, and surgical management of symptomatic leiomyomas. Discussion of the use of morcellation in the surgical management of leiomyomas is beyond the scope of this document and is addressed in a separate American College of Obstetricians and Gynecologists (ACOG) publication (3).

Background

Definition

Uterine leiomyomas are solid neoplasms composed of smooth muscle cells and fibroblasts. Leiomyomas vary in size and location. A standardized leiomyoma subclassification system was developed by the International Federation of Gynecology and Obstetrics (FIGO) to describe uterine leiomyoma location in relation to the endometrial and serosal surfaces (Fig. 1) (4).

Epidemiology

Uterine leiomyomas are common and estimated to occur in up to 70% of women by menopause (5). However, the true incidence and prevalence remain unknown because most cases are asymptomatic and likely go undiagnosed, with approximately only 25% being clinically significant enough to require intervention (5). The incidence of leiomyomas increases with age until menopause (6). Other factors that are associated with an increased risk of uterine leiomyomas include premenopausal status, family history, increasing interval since last birth, hypertension, and obesity (5, 7, 8). Factors that are associated with a decreased incidence of uterine leiomyomas include increasing parity and use of oral hormonal contraceptives or depot medroxyprogesterone acetate (DMPA) for any duration (5).

The prevalence rate of uterine leiomyomas is 2–3 times higher among Black women compared with White women (9, 10). The prevalence of uterine leiomyomas does not appear to be higher among Latina and Asian women as compared with White women, but data are far more limited for these populations (10).

Marked differences exist in disease presentation, severity, treatment, outcomes, and quality of life for Black women compared with White women with uterine leiomyomas. Black women typically develop uterine leiomyomas at an earlier age, are more likely to be anemic, develop clinically significant disease at an earlier age, and have larger uteri at the time of diagnosis (11–13). These observed differences are likely due in large part to systemic racism, as well as to social determinants of health. For instance, U.S.-born Black women who self-report experiencing racism have an increased risk of uterine leiomyomas (14). Experiences of racism can delay women from seeking care for leiomyoma symptoms until they are severe, and racial bias in medicine at the systemic and individual levels may affect the quality of diagnosis and treatment they receive (14). In

2023 CPT Code Review
Suprachoroidal Injections

Plain Language Summary:

Coverage question: Should OHP cover a certain way to deliver medication to the back of the eye?

Should OHP cover this treatment? Yes, for treatment of a condition where there's swelling in the center part of the eye (the macula) caused by inflammation (uveitic macular edema).

Code: **67516** Suprachoroidal space injection of pharmacologic agent (separate procedure)

Information: Current drug delivery techniques to access the posterior segment of the eye include intra-vitreal injections, peri-ocular injections (i.e., subconjunctival, subtenon, or juxtascleral), and intra-vitreal implants. Drug delivery by injection into the suprachoroidal space is another technique that has recently been proposed in the treatment of posterior segment disease. The suprachoroidal space provides a potential route of access from the anterior region of the eye to the posterior region. The suprachoroidal space (SCS), an anatomical niche nestled between the sclera and the choroid, provides a minimally invasive conduit for precise medication delivery.

Current Prioritized List status:

Uveitis is on line 360 CHORIORETINAL INFLAMMATION

Retinal (macular) edema is on line 449 DEGENERATION OF MACULA AND POSTERIOR POLE

Evidence

Wu 2023, review of suprachoroidal injection

i. N=8 studies on use in macular edema secondary to non-infectious uveitis which represented 2 phase III trials [PEACHTREE—sham controlled RCT; single arm phase III trial AZALEA], and 3 phase I/II trials
    1. PEACHTREE trial—160 eyes randomized to suprachoroidal triamcinolone acetonide (SCTA) or sham injection
        a. showed the significant improvement in visual acuity at 24 weeks and reduction in retinal central subfield thickness (CST), all without increasing the risk of elevated IOP or accelerated cataract progression.
ii. Studies on diabetic macular edema were all phase I/II trials or case series
iii. Studies on macular edema secondary to retinal vein occlusion included mostly phase II trials or case series
    1. One phase III trial showed no benefit compared to sham [SHAPPHIRE]

iv. Studies on post-operative/pseudophakic cystoid macular edema were all phase II trials or case series
v. Studies on photoreceptor loss were animal studies with 3 phase I trials

Expert guidelines
None identified

Other payer policies

1) Aetna 2022
    a. Aetna considers suprachoroidal injection (i.e., triamcinolone acetonide injectable suspension [Xipere]) medically necessary for the treatment of macular edema associated with uveitis when criteria are met. Aetna considers suprachoroidal injection of all other pharmacologic agents experimental and investigational for all indications because the effectiveness of this approach has not been established.
2) Cigna 2023
    a. Covers suprachoroidal injection of triamcinolone acetonide for macular edema associated with uveitis
3) Capital BCBS 2023
    a. Suprachoroidal delivery of a pharmacologic agent is considered investigational, as there is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

HERC staff summary
Suprachoroidal injections or triamcinolone have shown positive results in uveitic macular edema in one RCT as well as phase II trials. Private insurers coverage of these injections vary.

HERC staff recommendations:

a. Add CPT **67516** (Suprachoroidal space injection of pharmacologic agent (separate procedure)) to line 360 CHORIORETINAL INFLAMMATION
b. Add a new guideline as shown below to line 360

GUIDELINE NOTE XXX SUPRACHOROIDAL INJECTION
Line 360
Suprachoroidal space injection (CPT 67516) is only included on this line for treatment of macular edema associated with uveitis with triamcinolone acetonide.

pharmaceuticals

Review

Suprachoroidal Injection: A Novel Approach for Targeted Drug Delivery

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Abstract: Treating posterior segment and retinal diseases poses challenges due to the complex structures in the eye that act as robust barriers, limiting medication delivery and bioavailability. This necessitates frequent dosing, typically via eye drops or intravitreal injections, to manage diseases, often leading to side effects with long-term use. Suprachoroidal injection is a novel approach for targeted drug delivery to the posterior segment. The suprachoroidal space is the region between the sclera and the choroid and provides a potential route for minimally invasive medication delivery. Through a more targeted delivery to the posterior segment, this method offers advantages over other routes of administration, such as higher drug concentrations, increased bioavailability, and prolonged duration of action. Additionally, this approach minimizes the risk of corticosteroid-related adverse events such as cataracts and intraocular pressure elevation via compartmentalization. This review focuses on preclinical and clinical studies published between 2019 and 2023, highlighting the potential of suprachoroidal injection in treating a variety of posterior segment diseases. However, to fully harness its potential, more research is needed to address current challenges and limitations, such as the need for technological advancements, refinement of injection techniques, and consideration of cost and accessibility factors. Future studies exploring its use in conjunction with biotech products, gene therapies, and cell-based therapies can lead to personalized treatments that can revolutionize the field of ophthalmology.

Keywords: ophthalmology; ocular diseases; drug delivery; controlled drug release; retina; posterior segment diseases; ocular drug bioavailability; suprachoroidal injection

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1. Introduction

The landscape of ocular drug delivery is in constant evolution, presenting new challenges and opportunities in the field of ophthalmology. Treating posterior segment and retinal diseases is particularly challenging due to the eye's complex structures that act as barriers to drug delivery and bioavailability [1]. Traditional administration methods, such as eye drops, periocular and intravitreal (IV) injections, and systemic medications, often require frequent dosing and can result in substantial side effects with long-term use [2]. Recently, suprachoroidal (SC) injection has emerged as a novel strategy for targeted drug delivery to the posterior segment of the eye, offering an innovative approach to address these challenges [3].

The suprachoroidal space (SCS), an anatomical niche nestled between the sclera and the choroid, provides a minimally invasive conduit for precise medication delivery. This approach not only enhances drug concentrations in the posterior segment, increasing drug bioavailability and duration of action but also minimizes the risk of corticosteroid-related adverse events through compartmentalization [4]. The potential of SC injection has been highlighted by promising results from recent preclinical and clinical studies.

2023 CPT Code Review
Coronary Lithotripsy

Plain Language Summary:

Coverage question: Should OHP cover a medical procedure to help open blocked blood vessels to the heart?

Should OHP cover this treatment? No. It has not been compared to more common treatments and no studies found evidence of it working well.

Code: **92972** Percutaneous transluminal coronary lithotripsy (List separately in addition to code for primary procedure)

Additional code: HCPCS **C1761** Catheter, transluminal intravascular lithotripsy, coronary

Information: Coronary artery disease (CAD) is a condition in which there is insufficient blood flow in the arteries that feed the heart. CAD can be treated with percutaneous interventions such as coronary artery stenting. Calcium frequently builds up in the coronary arteries and makes interventions like stenting more difficult. To help stent deployment in these cases, several specialty balloons have been developed which cut or score the calcium lining the artery. Intravascular lithotripsy (IVL) is a recently introduced therapeutic modality in managing calcified coronary lesions (CCL). Lithotripsy enhances the fragmentation of CCL via delivery of circumferential sonic pressure waves to the vessel wall and applying pulsatile shockwaves to the surrounding plaque.

A description of this procedure from the NICE review:

> A percutaneous guidewire is passed from the radial or femoral artery into a coronary artery. Then, an intravascular lithotripsy catheter with embedded emitters enclosed in an integrated angioplasty balloon is passed and connected to an external generator with a connector cable. The catheter is advanced to the target lesion guided by radiopaque markers on the catheter. The balloon is then inflated with a saline and contrast solution to ensure contact with vessel wall. The lithotripsy cycle is then activated. For every cycle, the catheter emits localized, high-energy, pulsatile, unfocused, circumferential, acoustic, sonic, pressure waves (lasting microseconds). These waves pass through the inflated balloon into the wall of the coronary artery. As the waves travel along the wall and the connective tissue, they disrupt calcium deposits (both intimal and medial calcium) by microfracturing the calcified lesions. The cycle can be repeated until the lesion has been expanded sufficiently to allow optimal stent placement and optimization. Intravascular lithotripsy during PCI may improve stent delivery and expansion and modify focal intravascular calcium, while limiting localized injury to the endovascular surface.

Evidence

NICE 2020, evidence review intravascular lithotripsy for calcified coronary arteries during percutaneous coronary intervention

1) Included 3 studies
    1. DISRUPT CAD I study, case series of 60 patients
    2. DISRUPT CAD II study, case series of 120 patients
    3. Case series of 71 patients
2) Clinical success found in 94-95% of patients (defined as residual diameter stenosis of less than 50% after stenting without in-hospital major adverse cardiac event)
3) Safety
    1. In the case series of 60 patients, cardiac death (not related to the device) was reported in 3% (2/60) of patients
    2. In the case series of 120 patients, cardiac death (14 days after treating a 95% lesion in the distal right coronary artery because of probable stent thrombosis) was reported in 1 patient
    3. In the case series of 54 patients, cardiac death as a result of ST-elevation myocardial infarction complicated by cardiogenic shock in catheter lab was reported in 1 patient
    4. Deep arterial dissection due to angioplasty (type B according to the National Heart Lung and Blood Institute) occurred in 13% (4/31) of patients in the subgroup analysis of the DISRUPT CAD study of 31 patients
    5. Deep arterial dissection after IVL and stenting (type B and C) was reported in 1 patient each in the case series of 120 patients (DISRUPT CAD II study)
4) Freedom from MACE at 30 days
    1. In the case series of 60 patients, 95% (57/60) of patients did not have MACE at 30 days. However, 5% (3/60) of patients had asymptomatic non-Q-wave periprocedural myocardial infarctions
    2. In the case series of 120 patients, 94% (113/120) of patients reported no MACE in-hospital. However, 6% (7/120) of patients had asymptomatic non-Q-wave periprocedural myocardial infarctions. All these were not related to the device but involved elevated cardiac biomarkers. At 30 days, 8% (9/119) of patients reported non-Q wave myocardial infarctions, 1 patient reported Q wave myocardial infarction and 1 patient needed target vessel revascularisation. Stent thrombosis (definite or probable) was reported in 2% (2/120) of patients
    3. In the case series of 71 patients, 1 patient reported MACE at 30 days and unstable angina was reported in 1 patient after 7 days

Mhanna 2022, systematic review and meta-analysis of intravascular lithotripsy in calcified coronary lesions

1) N=8 studies (980 patients)
    a. 6 prospective cohort studies, 2 retrospective cohort studies
2) The clinical success was achieved in 95.4% of patients (95% CI: 92.9%–97.9%) and angiographic success was achieved in 97% of patients (95% CI: 95%–99%).
    a. clinical success which was defined as the ability of IVL to produce residual diameter stenosis < 50%) after stenting with no evidence of in-hospital major adverse cardiac events and target lesion revascularization

   b. angiographic success which was defined as success in facilitating stent delivery with RDS <50% and without serious angiographic complications
3) Coronary dissections (more than type B) were observed in 0.5% (95%CI: 0.0%–1.0%) and perforations were observed in 0.4% of the cases (95%CI: 0.0%–0.9%), and the 30-days MACE occurred in 4.9% (95%CI: 2.5%–7.3%) of the cases.
4) Conclusion: IVL seems to have excellent efficacy and safety in the management of severe CCL lesions. However, adequately powered RCTs are needed to evaluate IVL compared to other calcium/plaque modifying techniques.

Expert guidelines

ACC/AHA/SCAI 2021 guideline for coronary artery revascularization

1) In patients with fibrotic or heavily calcified lesions, plaque modification with orbital atherectomy, balloon atherotomy, laser angioplasty, or intracoronary lithotripsy may be considered to improve procedural success [2b (weak recommendation), level of evidence B-NR (moderate quality evidence from 1 or more well designed nonrandomized studies)]
2) Despite promising results from hundreds of small mechanistic studies, dozens of large, randomized trials have shown that the routine use of atheroablative devices does not improve clinical or angiographic outcomes. However, the use of atheroablative devices may enhance procedural success in specific circumstances
3) Intracoronary lithotripsy listed as a "potentially emerging modality"

Other payer policies

a. NICE 2020
   a. Evidence on the safety and efficacy of intravascular lithotripsy for calcified coronary arteries during percutaneous coronary intervention is limited in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research
b. Aetna 2023
   a. Intravascular shockwave lithotripsy for the treatment of coronary artery plaques is experimental
c. Cigna 2023
   a. Percutaneous transluminal coronary lithotripsy is experimental

Expert input:

Dr. Abigail Khan and Dr. David Saenger are not aware of its use in Oregon and do not recommend coverage.

2023 CPT Code Review
Coronary Lithotripsy

HERC staff summary

Intravascular coronary artery lithotripsy has been studied only in cohort studies. No studies exist comparing lithotripsy to other types of coronary artery stenting procedures which report on outcomes such as avoidance of major adverse cardiac events (MACE). A recent NICE review found evidence of harms, although it is unknown how these rates of harm compare to other types of coronary artery interventions. A highly trusted evidence source (NICE) did not find sufficient evidence of effectiveness for this procedure. Private insurers are not covering this procedure currently.

HERC staff recommendations:

a. Place CPT **92972** (Percutaneous transluminal coronary lithotripsy (List separately in addition to code for primary procedure)) and HCPCS **C1761** (Catheter, transluminal intravascular lithotripsy, coronary) on line 662
b. Add an entry to GN173 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 662

The following Interventions are prioritized on Line 662 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
92972, C1761	Coronary intravascular lithotripsy	Insufficient evidence of effectiveness	November 2023

2023 CPT Code Review
Enhanced Liver Fibrosis (ELF) Test

Plain Language Summary:

Coverage question: Should OHP cover a certain test to check on the health of the liver?

Should OHP cover this treatment? Maybe, this is one good way to test for advanced liver disease but costs more than other tests.

Code: **81517** Liver disease, analysis of 3 biomarkers (hyaluronic acid [HA], procollagen III amino terminal peptide [PIIINP], tissue inhibitor of metalloproteinase 1 [TIMP-1]), using immunoassays, utilizing serum, prognostic algorithm reported as a risk score and risk

Information: Liver diseases can cause liver damage, which is seen as fibrosis. This damage can result in cirrhosis of the liver. The Enhanced Liver Fibrosis (ELF) test is a blood test for fibrosis staging in chronic liver disease. Other testing options to assess for cirrhosis include fibroscan, blood tests, liver ultrasound and liver biopsy. Chronic liver disease can be caused by alcohol, obesity, or viral hepatitis. Liver biopsy is the gold standard test for liver fibrosis and cirrhosis, but it is invasive and can cause complications.

Previous HERC review
ELF was previously reviewed as part of the coverage guidance on non-invasive tests for liver fibrosis in 2016. The coverage guidance included a weak recommendation for coverage of ELF, but only if imaging tests (for example, elastography) were unavailable. The initially approved version of current guideline note 76 DIAGNOSTIC TESTING FOR LIVER FIBROSIS TO GUIDE MANAGEMENT IN CHRONIC LIVER DISEASE included coverage of ELF in that circumstance.

GN76 was addressed again in March 2019. At that time, ELF was reviewed and found to have "reasonable AUROC for distinguishing cirrhosis" but was identified as a proprietary lab test. Due to this proprietary test status, ELF was taken out of the guideline. "Given that there are a variety of good quality non-proprietary blood tests, additional expense associated with proprietary blood tests is not warranted."

Evidence
Sharma 2021, systematic review of accuracy of enhanced liver fibrosis test for diagnosing advanced liver fibrosis and cirrhosis

1) One author is an inventor of the ELF test and has conflicts of interest
2) N=36 studies (10 mixed causes of liver disease, 11 hepatitis C (HCV), 4 hepatitis B (HBV), 9 non-alcoholic fatty liver disease (NAFLD), 2 alcohol related liver disease)
    a. 31 prospective cohorts, 5 retrospective cohorts
    b. Reference standard was liver biopsy

3) HCV
    a. Advanced fibrosis: the AUROCs for detecting advanced fibrosis in HCV patients ranged from 0.773 (95% CI 0.697–0.848) to 0.98 (95% CI 0.93–1.00)
    b. Detecting cirrhosis: the sensitivity ranged from 7% to 100%. The specificity ranged from 53% to 100%
4) Hepatitis B
    a. Advanced fibrosis: the AUROCs ranged from 0.69 (95% CI 0.63–0.75) to 0.86 (95% CI 0.81–0.92)
    b. Cirrhosis: the AUROCs ranged from 0.706 0.68 (95% CI 0.61–0.75) to 0.86 (95% CI 0.81–0.92).
5) NAFLD
    a. The AUROCs for detecting advanced fibrosis in NAFLD patients ranged from 0.78 (0.70–0.89) to 0.97 (no CI reported)
    b. Only 2 studies reported the AUROCs for detecting cirrhosis in NAFLD patients which were 0.852 ± 0.040 in Guillaume et al. and 0.92 (0.88–0.97) in Staufer et al
6) Alcohol liver disease
    a. Advanced fibrosis: The AUROC was excellent ranging from 0.92 (0.89–0.96) in the Thiele et al. study and in the Madsen et al. study (0.88–0.96) to 0.944 (0.836–1.000).
    b. Two studies assessed the diagnostic accuracy of ELF at detecting cirrhosis reporting an excellent AUROC ranging from 0.93 (0.90–0.97) to 0.94 (0.91–0.97)
7) Mixed causes of liver disease
    a. Advanced fibrosis: The AUROCs reported in the included studies ranged widely from 0.63 (no CI) to 0.91 (0.88–0.95)
    b. Cirrhosis: All of the AUROCs reported were above 0.80, with the exception of one article, conducted in 280 patients with viral hepatitis, which reported an AUROC of 0.698 (no sensitivity or specificity reported)
8) In summary, the ELF test showed good diagnostic performance in detecting advanced fibrosis in patients with viral hepatitis and excellent performance in NAFLD and ALD. There is also evidence of good diagnostic performance for detecting cirrhosis in patients with viral hepatitis and excellent performance in patients with ALD. The quality of studies in HBV and ALD patients was very high, but more variable for HCV and NAFLD patients. This review suggests that the ELF test could offer an alternative to biopsy for assessing liver fibrosis in viral hepatitis, NAFLD, and ALD. However, the included studies were significantly heterogeneous, and further comparative studies of high methodological quality are desirable. The ELF test also offers other benefits such as lack of operator variability, excellent pre-analytical and analytical performance, and the very low failure rate

NICE 2016, evidence review for management of non-alcohol fatty liver disease (NAFLD)

1) Ten studies reported diagnostic test accuracy for diagnosing any fibrosis (greater than or equal to F1). Evidence was found on the following tests: enhanced liver fibrosis score (ELF) at thresholds of -0.207 and 9.28; Ferritin at thresholds ranging from 208 to 600; magnetic resonance elastography (MRE) at a threshold of 3.02; NAFLD fibrosis score at thresholds of −1.455 and 0.676; and transient elastography at thresholds ranging from 4.3 to 7.4

<u>Expert guidelines</u>

2023 CPT Code Review
Enhanced Liver Fibrosis (ELF) Test

American Association for the Study of Liver Diseases 2023, practice guideline for management of nonalcoholic fatty liver disease

1) ELF listed as an option for detection of advanced fibrosis and diagnosis of cirrhosis
2) ELF ≥11.3 is associated with increased risk of hepatic decompensation among patients with cirrhosis
3) FIB-4 is the most validated biomarker for estimation of liver fibrosis on patients with NAFLD
4) Although FIB-4 is statistically inferior to other serum-based fibrosis markers such as the ELF panel, FIBROSpect II, and imaging-based elastography methods to detect advanced fibrosis, FIB-4 is still recommended as a first-line assessment for general practitioners and endocrinologists based on its simplicity and minimal, if any, added cost
5) An ELF score of ≥9.8 reliably identifies patients with NAFLD at increased risk of progression to cirrhosis and liver-related clinical events
6) Such serum-based fibrosis tests [including ELF] may be good options as secondary risk assessments when elastography is not available
7) If FIB-4 is ≥ 1.3, VCTE, MRE, or ELF may be used to exclude advanced fibrosis
8) Highly elevated liver stiffness, FIB-4, and ELF scores can predict an increased risk of hepatic decompensation and mortality.

American Association of Clinical Endocrinology and the American Association for the Study of Liver Diseases 2022 guideline on the management of NAFLD

1) Clinicians should use liver fibrosis prediction calculations to assess the risk of NAFLD with liver fibrosis. The preferred noninvasive initial test is the FIB-4. Grade B; Intermediate Strength of Evidence; Best evidence level (BEL) 2
2) Clinicians should consider persons belonging to the "high-risk" groups (as defined under R2.1.1) who have an indeterminate or high FIB-4 score for further workup with an LSM (transient elastography) or ELF test, as available. Grade B; Intermediate Strength of Evidence; BEL 2

American Association for the Study of Liver Diseases and infectious Diseases Society of America 2022 recommendations on managing hepatitis C

1) Available at https://www.hcvguidelines.org/evaluate/testing-and-linkage
    a. Accessed October 6, 2023
2) Enhanced liver fibrosis testing is not mentioned
3) Recommends FIB4, APRI blood tests and transient elastography

<u>Other payer policies</u>

1) NICE 2016 management of non-alcoholic fatty liver disease
    a. Consider using the enhanced liver fibrosis (ELF) test in people who have been diagnosed with NAFLD to test for advanced liver fibrosis.
2) Aetna 2023
    a. Aetna considers the Enhanced Liver Fibrosis (ELF) test medically necessary for the detection and prognosis of liver fibrosis in persons with chronic liver diseases. Performance of the Enhanced Liver Fibrosis (ELF) test more than twice per year is considered not medically necessary. Performance of this test within 6

months following a liver biopsy (or other test for liver fibrosis) is considered not medically necessary.

3) Regence BCBS 2023
    a. Considers Enhanced Liver Fibrosis™ (ELF) Test to be investigational
4) Anthem BCBS 2023
    a. Proprietary algorithms evaluating hepatic fibrosis, used to produce a predictive score indicating the probability of liver fibrosis, are considered **investigational and not medically necessary** in the diagnosis and monitoring of individuals with chronic liver disease, including but not limited to hepatitis C, hepatitis B, and nonalcoholic fatty liver disease (NAFLD).

Expert input

Dr. Atif Zaman, hepatologist at OHSU

ELF as a fibrosis assessment tool and an approach to its use in light of all the other non-invasive assessment tools. Since these non-invasive tools to assess hepatic fibrosis have similar performance in most types of liver disease, it should be fine to consider the ELF approach for HCV

2023 CPT Code Review
Enhanced Liver Fibrosis (ELF) Test

HERC staff summary

The ELF test is one option in detecting advanced liver disease from a variety of causes. It was previously reviewed as part of a non-invasive testing for liver fibrosis coverage guidance and found to have evidence of effectiveness and was covered from 2016 to 2019. Coverage was removed a few years later due to the test being proprietary and thus of higher cost that other available similar tests. Of note, there was no CPT category 1 code for the ELF test during this time period.

ELF is recommended as one option for evaluation of NAFLD. Private insurers vary on coverage of this test. Alternative testing (liver biopsy, transient elastography) is covered on the Prioritized List. Expert guidelines recommend the use of the ELF test if elastography is not available to identify patients at increased risk of progression to cirrhosis and liver-related clinical events. A highly respected evidence based source (NICE) recommends using ELF in the management of nonalcoholic fatty liver disease.

HERC staff recommend coverage in certain circumstances based on expert input and previous coverage guidance review. The HERC may consider continued non-coverage due to the proprietary nature of the test and lack of consistent private payer coverage.

HERC staff recommendations:

1) **Option 1:**
    1. Place CPT **81517** (Liver disease, analysis of 3 biomarkers (hyaluronic acid [HA], procollagen III amino terminal peptide [PIIINP], tissue inhibitor of metalloproteinase 1 [TIMP-1]), using immunoassays, utilizing serum, prognostic algorithm reported as a risk score and risk) to line 198 CHRONIC HEPATITIS; VIRAL HEPATITIS
        a. Will pair with ICD-10-CM K75.81 (Nonalcoholic steatohepatitis (NASH)) and other hepatitis diagnosis codes
        b. Liver elastography (CPT 91200) is on line 198
    2. Modify GN76 as shown below

GUIDELINE NOTE 76, DIAGNOSTIC TESTING FOR LIVER FIBROSIS TO GUIDE MANAGEMENT IN CHRONIC LIVER DISEASE

Line 198

The following tests are included on this line because of their ability to effectively distinguish F4 from lower levels of fibrosis:

Non-proprietary blood tests:

- Platelet count
- Hyaluronic acid
- Age-platelet index
- AST-platelet ratio
- FIB-4
- FibroIndex
- Forns index
- GUCI
- Lok index

- Proprietary blood test:
  - Enhanced Liver Fibrosis (ELF™), for patients with indeterminate or high FIB-4 score when liver elastography is not available.

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

The following tests are not included on this line (or any other line):
- Real time tissue elastography
- Proprietary blood tests such as:
  - ~~Enhanced Liver Fibrosis (ELF™)~~
  - Fibrometer™
  - FibroTest®
  - Hepascore®
  - FIBROSpect® II

Noninvasive tests for liver fibrosis are only indicated for the initial assessment or when monitoring progression from F3 to F4, no more than annually.

Magnetic resonance elastography is included on this line for patients when ALL of the following apply:
- In whom at least one imaging test (FibroScan, ARFI, and SWE) has resulted in indeterminant results, a second one is similarly indeterminant, contraindicated or unavailable
- The patient is suspected to have aggressive disease/advanced fibrosis (e.g. in NAFLD based on older age, diabetes, obesity, high FIB-4, or APRI)
- Cirrhosis is not identified on routine imaging (ultrasound, CT)
- A liver biopsy would otherwise be indicated, but MRE would be an appropriate alternative.

Repeat MR Elastography is not indicated.

2) **Option 2**: continue lack of coverage
   1. Place CPT **81517** (Liver disease, analysis of 3 biomarkers (hyaluronic acid [HA], procollagen III amino terminal peptide [PIIINP], tissue inhibitor of metalloproteinase 1 [TIMP-1]), using immunoassays, utilizing serum, prognostic algorithm reported as a risk score and risk) to line 502 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS
   2. Add an entry to GN172 as shown below

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

Line 502

The following interventions are prioritized on Line 502 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS:

Procedure Code	Intervention Description	Rationale	Last Review
81517	Enhanced Liver Fibrosis (ELF™)	More costly than equally effective tests	November 2023

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PRACTICE GUIDANCE

AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease

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PREAMBLE

The study of NAFLD has intensified significantly, with more than 1400 publications since 2018, when the last American Association for the Study of Liver Diseases (AASLD) Guidance document was published.[1] This new AASLD Guidance document reflects many advances in the field pertinent to any practitioner caring for patients with NAFLD and emphasizes advances in noninvasive risk stratification and therapeutics. A separate guideline focused on the management of patients with NAFLD in the context of diabetes has been written jointly by the American Association of Clinical Endocrinology and AASLD.[2] Given the significant growth in pediatric NAFLD, it will not be covered here to allow for a more robust discussion of the diagnosis and management of pediatric NAFLD in the upcoming AASLD Pediatric NAFLD Guidance. A "Guidance" differs from a "Guideline" in that it is not bound by the Grading of Recommendations, Assessment Development and Evaluation system. Thus, actionable statements rather than formal recommendations are provided herein. The highest available level of evidence was used to develop these statements, and, where high-level evidence was not available, expert opinion was used to develop guidance statements to inform clinical practice. Key points highlight important concepts relevant to understanding the disease and its management.

The most profound advances in NAFLD relevant to clinical practice are in biomarkers and therapeutics. Biomarkers and noninvasive tests (NITs) can be used

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AI, artificial intelligence; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristic curve; BMI, body mass index; CAP, controlled attenuation parameter; CKD, chronic kidney disease; cT1, corrected T1; CVD, cardiovascular disease; DM, diabetes mellitus; DNL, de novo lipogenesis; DPP-4, dipeptidyl peptidase-4; ELF, Enhanced Liver Fibrosis; FAST, FibroScan-AST; FDA, US Food and Drug Administration; FIB-4, fibrosis-4 index; GH, growth hormone; GLP-1RA, glucagon-like peptide-1 receptor agonist; LDL-C, LDL cholesterol; LSM, liver stiffness measurement; MAST, score derived from MRI-PDFF, MRE, and serum AST; MEFIB, MRE combined with FIB-4; MRE, magnetic resonance elastography; NIT, noninvasive test; OSA, obstructive sleep apnea; PCOS, polycystic ovarian syndrome; PDFF, proton density fat fraction; PIVENS, Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with NASH; RCT, randomized controlled trial; SGLT-2, sodium glucose cotransporter-2; T2DM, type 2 diabetes mellitus; *TM6SF2*, transmembrane 6 superfamily member 2; UDCA, ursodeoxycholic acid; VCTE, vibration-controlled elastography

Brent A. Neuschwander-Tetri and Rohit Loomba are co-senior authors.

one approach over the over needs to be determined and the relative importance of point-of-care access weighed in depending on the context of use (Table 5).

Guidance statements:

17. Although standard ultrasound can detect hepatic steatosis, it is not recommended as a tool to identify hepatic steatosis due to low sensitivity across the NAFLD spectrum.

18. CAP as a point-of-care technique may be used to identify steatosis. MRI-PDFF can additionally quantify steatosis.

19. If FIB-4 is $\geq$1.3, VCTE, MRE, or ELF may be used to exclude advanced fibrosis.

Key points:

- *Highly elevated liver stiffness, FIB-4, and ELF scores can predict an increased risk of hepatic decompensation and mortality.*

THE ROLE AND INTERPRETATION OF LIVER BIOPSY

Histological evaluation of NAFLD should provide three basic pieces of information: diagnosis, grading of necroinflammatory activity, and staging of fibrosis severity.[357] To adequately assess these features, biopsies obtained with a 16-G needle should be at least 1.5 cm in length but preferably 2–2.5 cm in length.[358] Good-quality sectioning and staining are also important. Within the spectrum of NAFLD there are several distinct patterns: the common zone 3 injury pattern of adult steatohepatitis, the zone 1 steatosis-fibrosis pattern observed most often in young children, and steatosis with or without mild inflammation that does not meet criteria for steatohepatitis. Reporting of severity includes description of the pattern and degree of steatosis, inflammation, ballooning changes, and fibrosis.[357] Although fibrosis stage is the best predictor of long-term outcome in multivariable analyses,[30,36] ballooning injury and portal inflammation are short-term predictors of fibrosis progression or regression and are commonly combined as measures of disease grade[359,360] (Figure 3). Composite histological scores such as the NAFLD activity score (NAS) and the steatosis, activity, fibrosis score combine histological features and are used in clinical studies to offer a structured overall assessment of severity.[361,362] Biopsy remains the best method for providing information on the architectural distortion and the complex anatomic interrelationships of cellular injury, inflammation, and fibrosis.

Image analysis by artificial intelligence (AI) can provide more granular detail of histological findings as well as quantification of features on a continuous scale rather than the semiquantitative scoring system available to human observers.[363,364] Evaluation of steatosis and fibrosis are the most developed of the AI algorithms because the physicochemical properties of lipid droplets and collagen allow for easier identification by machines. The inherent variability in the composition and character of lobular and portal inflammation as well as the spectrum of hepatocyte injury that is identified as ballooning presents more challenges in correct classification and quantification by AI algorithms but is under development.

TREATMENT

A healthy diet and regular exercise form the foundation of treatment for the vast majority of those with NAFLD.[365] Even if weight loss is not needed, improved diet composition and increased exercise promote cardiovascular health in addition to improved liver health and metabolic comorbidities. For optimization of associated metabolic comorbid disease, a multidisciplinary team of clinicians provides the best chance for success in reducing liver and cardiovascular morbidity and mortality in patients with NAFLD (Figure 4).[173,366] Some of the medications approved for commonly associated comorbidities such as T2DM and obesity have been studied in the context of NAFLD and may reduce liver enzymes or steatosis or improve liver histology. Therefore, medications with possible liver-related benefits should be considered when managing comorbidities (Table 5).[2]

Liver protective healthy behaviors (lifestyle intervention)

Weight loss

Even modest amounts of weight loss can be impactful, especially in those with milder disease. Weight loss of 3%–5% improves steatosis, but greater weight loss ($>$10%) is generally required to improve NASH and fibrosis.[262,367–370]

Achieving and sustaining weight loss is challenging. Sustained weight loss reduces adipose tissue stress and improves peripheral insulin sensitivity,[39] which can reduce the drive for liver injury in NASH (Figure 1). Few patients ($\leq$10%) achieve effective weight loss despite structured interventions at 1 year, and fewer than half of these maintain the weight lost 5 years after intervention,[367,371] highlighting the need for ongoing nutrition support through multidisciplinary care

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of intravascular lithotripsy for calcified coronary arteries during percutaneous coronary intervention

Coronary arteries (the main blood vessels supplying blood to the heart) can become narrowed or blocked with fatty deposits. At times, the fatty deposits contain calcium and the arteries become stiff (calcified). Usually, a thin wire is passed down the affected artery (percutaneously, that is, via an artery in the groin or arm), and a small balloon is inflated to widen the narrowed artery, squashing the fatty deposits against the arterial wall so that blood can flow freely. Sometimes a small wire mesh tube (stent) is also inserted in the artery and left in place to keep it open. In a lithotripsy procedure, the balloon used to stretch the artery contains a device that delivers ultrasound shock waves. These waves break up the hard deposits (lithotripsy) to make it easier to insert the stent and to avoid damaging the artery. Lithotripsy allows the stent to fully expand and reduces the chances of later heart problems that can be caused by stents which have not fully expanded.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in July 2019 (01-07-2019).

Procedure name

- Intravascular lithotripsy for calcified coronary arteries during percutaneous coronary intervention

Specialist societies

- British Cardiovascular Intervention Society (BCIS)
- British Cardiovascular Society (BCS)
- Royal College of Physicians (Edinburgh)
- Royal College of Surgeons (Edinburgh)
- Royal College of Physicians London
- The Royal College of Physicians and Surgeons of Glasgow

Description of the procedure

Indications and current treatment

Coronary artery calcification (intimal and medial calcifications) increases the complexity of percutaneous treatment strategies in coronary interventions. It contributes to arterial wall stiffness, suboptimal stent delivery and expansion, in-stent restenosis, high rates of stent thrombosis and the need for subsequent target lesion revascularisation after endovascular interventions.

Standard endovascular treatment options for modifying calcification or plaques during percutaneous coronary intervention (PCI) include: balloon angioplasty using standard or super high-pressure non-compliant balloons; cutting or scoring

balloons; and stenting with or without coronary atherectomy (such as excisional, rotational, orbital or laser atherectomy). The aim of these treatments is to allow optimal stent expansion and achieve maximal luminal gain. However, they may sometimes lead to localised wall injury, balloon rupture or the risk of coronary vessel dissections or perforation.

More recently intravascular shockwave lithotripsy has become another endovascular therapeutic option for PCI.

What the procedure involves

In this procedure, shockwave intravascular lithotripsy is administered to the calcified coronary artery before stent deployment during PCI.

A percutaneous guidewire is passed from the radial or femoral artery into a coronary artery. Then, an intravascular lithotripsy catheter with embedded emitters enclosed in an integrated angioplasty balloon is passed and connected to an external generator with a connector cable. The catheter is advanced to the target lesion guided by radiopaque markers on the catheter. The balloon is then inflated with a saline and contrast solution to ensure contact with vessel wall. The lithotripsy cycle is then activated. For every cycle, the catheter emits localised, high-energy, pulsatile, unfocused, circumferential, acoustic, sonic, pressure waves (lasting microseconds). These waves pass through the inflated balloon into the wall of the coronary artery. As the waves travel along the wall and the connective tissue, they disrupt calcium deposits (both intimal and medial calcium) by microfracturing the calcified lesions.

The cycle can be repeated until the lesion has been expanded sufficiently to allow optimal stent placement and optimisation. Intravascular lithotripsy during PCI may improve stent delivery and expansion and modify focal intravascular calcium, while limiting localised injury to the endovascular surface.

Efficacy summary

Device or procedural success

In a case series of 60 patients (DISRUPT CAD I study) with severely calcified coronary arteries treated with intravascular lithotripsy (IVL) before stenting and PCI, the IVL balloon was delivered successfully in 98% (59/60) of patients and the stent in 100%.[1]

In a case series of 120 patients (DISRUPT CAD II study) with severely stenotic, calcified de novo coronary artery lesions treated with intravascular lithotripsy (IVL) for vessel preparation before stenting and PCI, the IVL balloon and stent were delivered successfully in all patients.[3]

In a case series of 71 patients with moderate to severely calcified coronary lesions (78 lesions) treated with IVL, there was successful device delivery and complete lithotripsy treatment to the target lesion in all patients.[4]

Clinical success

In the case series of 60 patients (DISRUPT CAD I study), clinical success was reported in 95% (57/60) of patients. Clinical success was defined as residual diameter stenosis of less than 50% after stenting without in-hospital major adverse cardiac event (MACE, defined as cardiac death, myocardial infarction or target vessel revascularisation).[1]

In the case series of 120 patients (DISRUPT CAD II study), clinical success was reported in 94% (113/120) of patients. Clinical success was defined as the ability of IVL to produce a diameter stenosis of less than 50% after stenting with no evidence of MACE.[3]

In the case series of 71 patients, success strategy (defined as successful delivery and expansion with less than 20% residual stenosis of target lesion, TIMI 3, no stent failure) was reported in 78% (61/78) of patients. Success strategy was reached in 85% (33/39) patients with primary IVL in native, severely calcified de novo lesions (39 lesions), in 77% (17/22) of patients with secondary IVL in lesions where non-compliant balloon dilation failed (22 lesions), and in 65% (11/17) of patients with tertiary IVL in lesions with stent under expansion after previous stenting (17 lesions).[4]

Angiographic outcomes

In the case series of 60 patients (DISRUPT CAD I study), median diameter stenosis (on angiography) was reduced from 73% (range 59% to 77%) at baseline to 12% (range 7% to 21%) at 6-month follow up. Also, minimum lumen diameter increased from 0.9 mm^2 (range 0.6 to 1.1 mm^2) to 2.6 mm^2 (range 2.3 to 2.9 mm^2), with an acute area gain of 1.7 mm^2 (range 1.3 to 2.1 mm^2) after coronary IVL and stenting.[1]

In the case series of 120 patients (DISRUPT CAD II study), angiographic success (defined as success in facilitating stent delivery, with less than 50% residual stenosis and freedom from perforation, slow flow, no flow or type D,E,F dissection at any point during the procedure) was reported in all patients. The residual stenosis after IVL was 9.4%, which further decreased to 7.8% after stent implantation. Also, minimum lumen diameter increased from 1.21 mm to 2.88 mm with an acute area gain of 1.67 mm after coronary IVL and stenting.[3]

A subgroup analysis of the DISRUPT CAD I study, which included 31 patients and assessed the performance of IVL on heavily calcified coronary lesions and stent placement using optical coherence tomography, showed a reduction in area

stenosis (from 67% to 40%), an increase in minimum lumen area (from 2.23 mm^2 to 4.16 mm^2) and an acute area gain of 2.08 mm^2 after IVL. The mean stent area was 8.37 mm^2 and mean stent expansion was 112% after stent deployment. Calcium modification was achieved after IVL in 43% (12/28) of lesions and after stenting in 55% (17/31) of lesions, with a high frequency of fractures per lesion in the heavily calcified lesions compared with the least calcified lesions (highest tertile versus lowest tertile; p=0.0009). There was also a greater incidence of calcium fracture in the highest calcification tertile (78% compared with 22%; p=0.057). Stent expansion was similar among all tertiles of calcification severity.[2]

A subgroup analysis of the DISRUPT CAD II study, which included 48 patients before IVL and 47 patients after stenting, reported that IVL statistically significantly increased minimal lumen area from 2.33 mm^2 to 6.10 mm^2 ($p<0.001$) after stent implantation and decreased calcium angle (from 175 to 127 degrees, p=0.05). Calcium fracture was identified in 79% (37/47) of lesions post IVL with multiple fractures in 55% (26/47) of lesions. Mean fracture length was 5.5 mm with 3.4 fractures per lesion and 1.6 fractures per frame. Maximum calcium thickness was 0.8 mm and angle at the calcium fracture site was 224 degrees. At pre-IVL maximum calcium site, mean calcium thickness decreased from 0.93 to 0.89 mm (p=0.004) and calcium angle decreased from 266 to 215 degrees ($p<0.0001$) after stent implantation. The acute area gain was 4.79 mm^2 and final stent expansion was 102%.[3]

In the case series of 71 patients, the mean diameter stenosis of calcified lesions at baseline was 71.8%, which decreased to 45% immediately after IVL and to 17.5% after stenting. Mean minimal lumen diameter was 1.01 mm at baseline, which increased to 1.90 mm after IVL and to 2.88 mm after stenting.[4]

In a case series of 26 patients with heavily calcified coronary arteries treated with IVL during PCI before stent deployment, there was angiographic success (less than 20% residual stenosis) in all patients.[6]

Safety summary

Cardiac death

In the case series of 60 patients, cardiac death (not related to the device) was reported in 3% (2/60) of patients.[3]

In the case series of 120 patients, cardiac death (14 days after treating a 95% lesion in the distal right coronary artery because of probable stent thrombosis) was reported in 1 patient.[3]

In the case series of 54 patients, cardiac death as a result of ST-elevation myocardial infarction complicated by cardiogenic shock in catheter lab was reported in 1 patient.[5]

Freedom from MACE at 30 days

In the case series of 60 patients, 95% (57/60) of patients did not have MACE at 30 days. However, 5% (3/60) of patients had asymptomatic non-Q-wave periprocedural myocardial infarctions.[1]

In the case series of 120 patients, 94% (113/120) of patients reported no MACE in-hospital. However, 6% (7/120) of patients had asymptomatic non-Q-wave periprocedural myocardial infarctions. All these were not related to the device but involved elevated cardiac biomarkers. At 30 days, 8% (9/119) of patients reported non-Q wave myocardial infarctions, 1 patient reported Q wave myocardial infarction and 1 patient needed target vessel revascularisation. Stent thrombosis (definite or probable) was reported in 2% (2/120) of patients.[3]

In the case series of 71 patients, 1 patient reported MACE at 30 days and unstable angina was reported in 1 patient after 7 days.[4]

Freedom from MACE at 6 months

In the case series of 60 patients, 92% (55/60) of patients did not have MACE at 6 months. However, 8% (5/60) of patients had complications, which included 3 asymptomatic non-Q-wave myocardial infarctions and 2 cardiac deaths (neither of which were related to the procedure).[1]

Dissections postintravascular lithotripsy

Deep arterial dissection due to angioplasty (type B according to the National Heart Lung and Blood Institute) occurred in 13% (4/31) of patients in the subgroup analysis of the DISRUPT CAD study of 31 patients. This was successfully treated with stent implantation.[2]

Deep arterial dissection after IVL and stenting (type B and C) was reported in 1 patient each in the case series of 120 patients (DISRUPT CAD II study). Both patients were managed conservatively.[3]

Coronary type B dissections without further sequelae were reported in 5% (4/78) of lesions in the case series of 71 patients.[4]

Device failure

Device failure (balloon rupture or bursting in complex lesions with no sequelae during treatment) was reported in 9% (7/78) of lesions in the case series of

71 patients. 4 of these were in patients with secondary IVL in lesions where a non-compliant balloon dilation failed (22 lesions), and 3 were in patients with primary IVL in native calcified de novo lesions (n=39).[4]

Ventricular capture

Ventricular capture (identified as a change in QRS morphology with the onset precisely coinciding with the electromagnetic 'spike' of the shockwave pulse-'shocktopics' and asynchronous cardiac pacing) was reported in 78% (42/54) of patients in the case series of 54 patients. Multivariable logistic regression analysis identified heart rate as the only independent predictor of an increased risk of IVL-induced ventricular capture. Patients with a heart rate of less than 65 beats per minute before IVL were 16 times more likely (OR 16.3, 95% confidence interval 2.4 to 110.8], p=0.004) to experience induced 'shocktopics' compared with patients who had a heart rate of 65 beats per minute or more.[5]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, specialist advisers listed the following anecdotal adverse events: IVL balloon rupture creating dissections, and IVL leading to PVC or transient V pacing. They considered that there were no theoretical adverse events.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to intravascular lithotripsy for calcified coronary arteries during PCI. The following databases were searched, covering the period from their start to 01-07-2019: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded in which no clinical outcomes were reported, or in which the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with calcified coronary arteries
Intervention/test	Intravascular lithotripsy during percutaneous coronary intervention
Outcome	Articles were retrieved if the abstract contained information relevant to the safety, efficacy or both.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 362 patients from 6 case series[1,2,3]. There is an overlap of patients between study 1 and 2.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in appendix A.

Table 2 Summary of key efficacy and safety findings on intravascular lithotripsy for calcified coronary arteries during percutaneous coronary intervention

Study 1 Briton TJ 2019

Details

Study type	Case series (cohort study -DISRUPT CAD I study -NCT02650128)
Country	Europe and Australia -5 countries (multicentre)
Recruitment period	2015-16
Study population and number	n=**60 patients with severely calcified coronary artery lesions needing revascularisation** Target vessel: left anterior descending artery (n=28), right coronary artery (n=23), circumflex artery (n=8), protected left main artery (n=2). Diameter stenosis 72.5% (range 58.5 to 77%); lesion length 18.2mm (range 14.1 to 25.4mm); calcified length 21mm; reference vessel diameter 3mm; lumen diameter 0.9 mm (range 0.6 to 1.1 mm^2); initial stenosis 68%.
Age and sex	Mean 72 years; 80% (48/60) male
Patient selection criteria	Patients with a clinical indication for coronary intervention needed to have more than 1 lesion needing PCI with a diameter stenosis more than 50%, a native coronary lesion less than 32 mm and heavy calcification defined as calcification within the lesion on both sides of the vessel assessed during angiography by the operator.
Technique	Coronary IVL followed by subsequent stent implantation and PCI at the discretion of the operator.
Follow up	**30 days and 6 months**
Conflict of interest/source of funding	Study sponsored by Shockwave medical. All authors received fees, grants from different companies. One author is a cofounder of the device and 1 author had equity in the company, and another author is a full-time employee of the company.

Analysis

Follow-up issues: short term follow up. Loss to follow up not reported.

Study design issues: prospective single-arm study in 7 hospitals. Primary efficacy end point was clinical success, defined as the ability of IVL to produce a diameter stenosis of less than 50% after stenting with no evidence of in-hospital MACE (cardiac death, myocardial infarction, or target vessel revascularisation). The primary safety end point was freedom from MACE through 30 days defined as cardiac death, myocardial infarction, or target vessel revascularisation.

Study population issues: severe calcification was present in all patients. Patients also had multiple comorbidities.

Other issues: there is an overlap of patients between study 1 and 2.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **60**

Efficacy outcomes

Clinical success %	95 (57/60)
Device success %	98 (59/60)
Stent delivery %	100 (60/60)
Final in-stent angiographic outcomes	
Mean minimum lumen diameter, mm	2.6 (range 2.3 to 2.9)
In-stent acute gain, mm	1.7 (range 1.3 to 2.1)
In-stent diameter stenosis reduced %	12 (range 7 to 21)
Patients with residual diameter stenosis <50% after stenting	100 (60/60)
Patients with residual diameter stenosis< 30% after stenting	92 (55/60)
Patients with residual diameter stenosis <20% after stenting	73 (44/60)

Safety

Adverse events

	%(n)
Grade D dissections (post IVL needed stenting, resolved at final angiography)	3.3 (2/60)
MACE at 30 days	**5 (3/60)**
Cardiac death	0
Non-Q-wave MI (involved elevated cardiac biomarkers, not related to the device)	5 (3/60)
Q-wave MI	0
TVR	0
MACE at 6 months	**8.5 (5)**
Cardiac death (not related to the device)	3 (2/60)
Non-Q-wave MI	5 (3/60)
Q-wave MI	0
TVR	0

No perforations, residual dissections, abrupt closure, slow flow or no reflow reported at follow up.

Abbreviations used: IVL, intravascular lithotripsy; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention; TVR, target vessel revascularisation.

Study 2 Ali ZA 2017

Details

Study type	Case series (sub-study of DISRUPT CAD I study NCT02471586)
Country	Europe and Australia in 5 countries, multicentre (7 hospitals)
Recruitment period	2015-2016
Study population and number	n=**31 patients having planned PCI for angina with severely calcified stenotic coronary de novo lesions** Target vessels: left anterior descending 14, circumflex 5, right coronary artery 12 severe calcification in 87% (27/31); lesion length: 21.7±11.6mm; calcification length: 21.3±10.3mm.
Age and sex	Mean 71 years; 80% (25/31) male
Patient selection criteria	Inclusion criteria: patients having planned PCI for stable or unstable angina or silent ischemia with severe calcification (assessed by angiography), single target lesions located in a native coronary artery with visually estimated reference vessel diameter of 2.5 to 4.0mm and length <32mm. Exclusion criteria: unprotected left main, planned concomitant use of atherectomy or speciality balloon, chronic total occlusions, and stent within 5mm of the lesion.
Technique	IVL (using Shockwave coronary lithoplasty system) done (with mean 2 lithoplasty balloons per lesion) for vessel preparation and subsequent metallic or drug-eluting stent placement done using OCT in all. A minimum of 20 pulses per target lesion were done, delivering mean 4 lithoplasty treatments (range 2 to 7). If lesion exceeded 12 mm balloon length, it was repositioned and lithoplasty repeated. PCI was done via femoral or radial access; anticoagulation, anti-platelet therapy and other medications given as per local standard of care.
Follow up	**Post procedure**
Conflict of interest/source of funding	Study designed and sponsored by the company as part of the DISRUPT CAD trial. All authors received fees, grants from different companies. One author is a cofounder of the device and 1 author had equity in the company, and another author is a full-time employee of the company.

Analysis

Follow-up issues: short follow-up period, loss to follow up not reported.

Study design issues: small multicentre prospective single-arm observational study, OCT done only in selected patients in the DISRUPT CAD I study, and findings were analysed; an independent clinical events committee judged all MACE and an independent laboratory analysed all imaging.

Study population issues: Patients had multiple comorbidities. Predilation was needed only in 6 patients.

Other issues: this is a sub-study of the DISRUPT CAD I study above (Brinton 219).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **31**

Angiographic outcomes (Mean±SD)

	Baseline	Post PCI
Reference vessel diameter, mm	2.87±0.99	2.96±0.47
Minimum lumen diameter, mm	0.99±0.41	2.51±0.35
Diameter stenosis %	65.1±14.4	13.9±12.5
Acute gain, mm		1.54±0.54
Stent length, mm		30.7±11.9

OCT imaging analysis

	Pre IVL (N=26)	Post IVL (N=28)	Post stent (N=31)	Final MSA site
Lesion length, mm	31.50±9.74	-	-	
Minimal lumen area, mm^2	2.23±1.11	4.16±1.86	5.99±1.97	
Mean lumen area mm^2	4.85±1.86	-	8.49±3.04	
Area stenosis %	66.50±11.30	39.80±24.20	20.50±20.30	
Acute area gain mm^2		2.08±1.65	3.69±1.52	2.36±1.88
Minimal stent area mm^2			8.37±3.17	5.94±1.98
Mean stent expansion mm^2			112.0±37.2	79.4±2.70

OCT features of calcium fracture

	Post IVL (n=28)	Post stent implantation (n=31)	P value
Calcium fracture %	43 (12/28)	55 (17/31)	0.08
Fracture depth mm	0.42±0.21	0.43±0.25	0.72
Fracture length mm	2.79±4.49	3.36±4.99	0.02
Fracture angle	20.50±19.50	29.50±33.70	0.06

Safety

No major intraprocedural complications or postoperative PCI sequalae.

Complications post lithotripsy	% (n)
Deep dissection >type B (NHLBI) because of angioplasty (treated with stent implantation)	13% (4/31)
Slow flow or no reflow	0
Abrupt closure	0
Perforation	0
Final complications post PCI	**0**

Calcium fractures per lesion	0.00	1.00	0.03
Multiple calcium fracture/frame	26 (7/28)	29 (9/31)	0.34

Effect of IVL according to tertiles of calcium severity

The frequency of calcium fractures per lesion increased in the most severely calcified plaques (highest tertile versus lowest tertile, p=0.009) with a trend towards a greater incidence of calcium fracture (77.8% versus 22.2%, p=0.057).

Abbreviations used: IVL, intravascular lithotripsy; MSA, minimal stent area; NHLBI, National Heart Lung Blood Institute; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; SD, standard deviation.

Study 3 Ali ZA 2019

Details

Study type	Case series (DISRUPT CAD II study -NCT03328949)
Country	US and Europe -9 countries
Recruitment period	2018-19
Study population and number	n=**120 patients with severely stenotic, calcified de novo coronary artery lesions needing revascularisation had vessel preparation for stent implantation with IVL** Target vessel: left anterior descending artery 62.5% (n=75), right coronary artery 25% (n=30), circumflex artery 11.7% (n=14) and protected left main artery 0.8% (n=1). Lesion characteristics: diameter stenosis 60±12.0%; lesion length 19.5±9.8 mm; calcified length 25.7±12.4mm; reference vessel diameter 3.04±0.53 mm; minimum lumen diameter 1.21±0.42 mm; severe calcification in 94.2% (113/120). 71% lesions were concentric and 30% had side branch involvement.
Age and sex	Mean 72 years; 78% (94/120) male
Patient selection criteria	Inclusion criteria: patients with silent ischemia, unstable or stable angina with evidence of myocardial ischemia, or stabilised acute coronary syndrome without elevation in cardiac biomarkers. Those with a single target lesion needing PCI with a diameter stenosis more than 50%, a native coronary lesion length less than 32 mm and severe calcification defined as calcification within the lesion on both sides of the vessel assessed during angiography as determined by the operators. Exclusion criteria: planned use of atherectomy, speciality balloons, or investigational coronary devices.
Technique	Coronary IVL followed by subsequent stent implantation and PCI was done at the discretion of the operator. PCI was performed via femoral or radial access. IVL catheter insertion done as described in procedure description section. Sometimes an adjunctive tool (a buddy wire, small balloon or guide catheter extension) is used in case of difficulty while passing the catheter over the lesion. Atherectomy was not permitted as per protocol. If lesion preparation is not complete after maximal number of pulses, then further IVL catheters (with similar or different diameters) were used. The mean number of IVL catheters used per lesion were 1.2. Pre-dilatation to deliver the IVL catheter was needed in 42% patients. Mean balloon size was 2.2 mm. Subsequent stent implantation and medications were administered as per standard protocol. A mean number of 1.3 drug eluting stents were implanted per patient and post dilation was needed in 79% patients.
Follow up	**30 days**
Conflict of interest/source of funding	Study was designed by principal investigators and sponsor (Shockwave medical Inc). The majority of authors received fees, grants, research support and honoraria from different companies. One author is a cofounder of the device and 1 author had equity in the company, and another author is a full-time employee of the company.

Analysis

Follow-up issues: short term follow up. Loss to follow up not reported.

Study design issues: small prospective, multicentre post-approval study done in 15 hospitals. Primary efficacy end point was in-hospital MACE (cardiac death, myocardial infarction, or target vessel revascularisation). Secondary end point was clinical success, defined as the ability of IVL to produce a diameter stenosis of less than 50% after stenting with no evidence of MACE. An OCT sub-study was done to evaluate the mechanism action of IVL, quantifying calcium characteristics and calcium fracture. Independent lab assessed angiography and OCT and an independent clinical events committee assessed MACE.

Study population issues: severe calcification was present in all patients. Patients also had multiple comorbidities.

Other issues: there is an overlap of patients between 3 studies (Brinton 2019 [disrupt CAD I study], Ali ZA 2017 [sub-study of CAD I study], Ali ZA 2019 [CAD II study]).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **120**

Procedure outcomes

Total procedure time, minutes	68.3±34.2
IVL treatment time, minutes	7.9±5.2

Efficacy outcomes

	n=120
Clinical success %	94.2 (113/120)
Angiographic success* %	100 (120/120)
Stent delivery %	100 (120/120)
Final in-segment angiographic outcomes	
Mean minimum lumen diameter, mm	2.83 ±0.48
In-stent acute gain, mm	1.63 ±0.49
Residual diameter stenosis %	9.4±7.5
Patients with residual diameter stenosis <50% after stenting	100 (120/120)
Patients with residual diameter stenosis < 30% after stenting	99.2 (119/120)
Final in-stent angiographic outcomes	
Mean minimum lumen diameter, mm	2.88 ±0.47
In-stent acute gain, mm	1.67 ±0.49
Residual diameter stenosis %	7.8±7.1
Patients with residual diameter stenosis <50% after stenting	100 (120/120)
Patients with residual diameter stenosis< 30% after stenting	100 (120/120)

**defined as success in facilitating stent delivery with<50% residual stenosis and freedom from perforation, slow flow, no reflow or type D,E,F dissection at any point during the procedure.*

OCT sub study analysis

	Pre IVL (n=48)	**Post Stent (n=47)**	**P value**
At pre-IVL minimal lumen area site			
Lesion length, mm	29.±9.8	-	-
Minimal lumen area, mm^2	2.33±1.35	6.10±2.17	<0.001
Calcium angle, degrees	175.8±96.9	127.1±97.6	0.055
Maximum calcium thickness	0.9±0.3	0.8±0.3	0.45
Calcium fracture %		1.9% (5/28)	
Acute area gain mm^2		3.99±1.72	

Safety

Adverse events

	% (n=120)
Dissections, type	
Grade B (post stent IVL managed conservatively)	0.8 (1/120)
Grade C (post stent IVL managed conservatively)	0.8 (1/120)
MACE in hospital	**5.8 (7/120)**
Non-Q-wave MI (involved elevated cardiac biomarkers, not related to the device)	5.8 (7/120)
MACE at 30 days	**7.6 (9/120)**
Cardiac death (14 days after treating a 95% lesion in the distal right coronary artery due to probable stent thrombosis)	0.8 (1/120)
Non-Q-wave MI (in hospital)	5.9 (7/120)
Q-wave MI	0.8 (1/120)
TVR	0.8 (1/120)
Stent thrombosis (definite or probable)	1.7 (2/120)

No perforations, abrupt closure, slow flow or no reflow reported at follow up.

stent area mm^2		6.06±2.20	
stent expansion %		79.1±2.1	
At pre IVL maximum calcium site	**n=48**	**n=38**	
Minimal lumen area, mm^2	3.64±1.78	8.47±3.04	<0.0001
Calcium angle, degrees	266.3±77.1	215.1±69.4	<0.0001
Maximum calcium thickness	0.93±0.2	0.89±0.2	0.004
Calcium fracture %		50% (19/38)	
Acute area gain mm^2		4.79±2.45	
stent area mm^2		7.77±2.65	
stent expansion %		102.8±30.6 (n=35)	
At final minimal stent area	**n=48**	**n=47**	
Minimal lumen area, mm^2	4.26±2.86	6.25±2.25	<0.0001
Calcium angle, degrees	176.6±100.4 (n=23)	149.4±94.8 (n=30)	0.0004
Maximum calcium thickness	1.0±0.3 (n=23)	0.9±0.3 (n=30)	0.055
Calcium fracture %		23.3% (7/30)	
Acute area gain mm^2		2.52±2.03 (n=35)	
stent area mm^2		5.92±2.14	
stent expansion %		77.6±20.5 (n=44)	

OCT features of calcium fracture by IVL

	Post IVL (n=47)
Calcium fracture %	78.7 (37/47)
Multiple fractures (> 2)	55.3 (26/47)
Fracture depth, mm	0.6±0.3 (n=37)
Fracture length, mm	5.5±5.0 (n=37)
Calcium fracture angle at the site, degrees	224.5±70.9
Maximum calcium thickness, mm	0.8±0.3
Calcium fractures per lesion, n	3.4±2.6
Multiple calcium fracture/frame, n	1.6±0.8 (7/28)

Abbreviations used: IVL, intravascular lithotripsy; MACE, major adverse cardiac events; MI, myocardial infarction; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; TVR, target vessel revascularisation.

Study 4 Aksoy A 2019

Details

Study type	Case series
Country	Germany (multicentre)
Recruitment period	2018
Study population and number	n=**71 patients with moderate to severely calcified coronary lesions (n=78) treated with IVL** Calcification %: (82 % (64/78) lesions were severely calcified, 18% (14/71) lesions were moderately calcified). Targeted vessels: left anterior descending artery (43.6%, n=34), right coronary artery (33%, n=26), ramus circumflexus (6.4%, n=5), left main artery (16.7%, n=13) Group A: primary IVL in native, severely calcified de novo lesions (n=39 lesions) Group B: secondary IVL in lesions where noncompliant balloon dilatation failed (n=22 lesions, 20 patients) Group C: tertiary IVL in lesions with stent under expansion after previous stenting (n=17 lesions)
Age and sex	Mean 76 years; 72% (51/71) male
Patient selection criteria	Patients with significant calcified coronary lesions and in-stent stenosis due to severe calcification were screened (based on the angiographic degree of calcification) for eligibility for IVL.
Technique	Intravascular lithotripsy (IVL using Shockwave coronary^2 balloon) done for vessel preparation and subsequent metallic or drug-eluting stent placement done. Coronary angiography was done as per conventional standards. Intracoronary nitroglycerin was administered before baseline. PCI was done during the same procedure or as a staged procedure. Post interventional antiplatelet therapy was given to all patients.
Follow up	**30 days**
Conflict of interest/source of funding	Study funded by clinical study research program at the University Hospital Bonn. 4 authors are principal or sub-investigators of the Disrupt CAD II study.

Analysis

Follow-up issues: very short follow-up period.

Study design issues: prospective observational registry data from 3 centres was assessed for the overall cohort and for each type of treatment (primary IVL therapy, secondary IVL and tertiary IVL). Primary end points were strategy success (defined as stent expansion with less than 20% in stent residual stenosis of target lesion in the presence of TIMI 3 flow without stent failure) and safety outcomes (procedural complications and in hospital MACE as proposed by American Heart Association and Academic Research Consortium 2). Data were collected by review of medical records and followed-up by telephone interview. Intravascular imaging was done in 50% (35/71) cases, 23 by ultrasound and 12 by OCT.

Study population issues: 46.5% patients had stable angina, 15.5% had unstable angina, 14% had non-ST segment elevation acute coronary syndromes and 14% had acute heart failure. Patients had cardiac risk factors such as hypertension, hypercholesterolemia and diabetes. There was no difference in baseline, procedural characteristics between the groups.

Other issues: in 6 patients mechanical circulatory support was used.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **71 (78 lesions)**

Efficacy outcomes

	Overall % (n=78)	Group A % (n=39)	Group B % (n=22)	Group C % (n=17)
Success strategy (successful delivery and expansion with <20% residual stenosis of target lesion, TIMI 3, no stent failure)	78.2 (61/78)	84.6 (33/39)	77.3 (17/22)	64.7 (11/17)
Successful device delivery and complete lithotripsy treatment of the target lesion	100 (78/78)	100 (39/39)	100 (22/22)	100 (17/17)

Angiography outcomes (OCT analysis)

	Baseline (mean±SD)	Post IVL (mean±SD)	Post PCI (mean±SD)
Overall cohort			
Reference vessel diameter, mm		3.51±0.46	
Minimal lumen diameter, mm	1.01±0.49	1.90±0.61	2.88±0.56 (p<0.001)
Acute gain, mm	-	0.89±0.76	1.87±0.60
Diameter stenosis %	71.8±13.1	45.1±17.4	17.5±15.2
Group A			
Reference vessel diameter, mm		3.58±0.46	
Minimal lumen diameter, mm	1.1±0.46	1.85±0.63 (p=0.01)	2.94±0.56 (p<0.0001)
Acute gain, mm	-	0.75±0.60	1.84±0.57
Diameter stenosis %	69.45±13.25	46.34±18.28	16.98±14.23
Group B			
Reference vessel diameter, mm		3.49±0.50	
Minimal lumen diameter, mm	1.05±0.56	2.17±0.56	2.81±0.51 (p<0.01)

Safety

Safety outcomes

	Overall % (n=78)	Group A % (n=39)	Group B % (n=22)	Group C % (n=17)
Device failure (balloons burst in complex lesions/ ruptured with no sequelae)	9 (7/78)	7.7 (3/39)	18.2 (4/22)	0
In hospital MACE	0	0	0	0
Unstable angina (after 7 days)	1.3 (1/78)			
30 days MACE (MI, TVF, or cardiac death)	1.3 (1/78)	0	0	11.1 (1/17)
Coronary dissection, type B, without further sequelae	5.1 (4/78)	7.7 (3/39)	5.9 (1/22)	0

Perforations, slow flow, reflow, or abrupt vessel closure did not occur in any treated lesions.

Acute gain, mm	-	1.12±0.92	1.81±0.65	
Diameter stenosis %	71.0±13.29	41.69±17.47	19.0±13.09	
Group C				
Reference vessel diameter, mm		3.5±0.46		
Minimal lumen diameter, mm	0.77±0.39	1.88±0.53	2.78±0.57 (P<0.001)	
Acute gain, mm	-	1.11±0.56	2.01±0.68	
Diameter stenosis %	77.3±10.47	45.04±15.53	20.33±16.93	

Abbreviations used: IVL, intravascular lithotripsy; MACE, major adverse cardiac events; MI, myocardial infarction; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; SD, standard deviation; TIMI, thrombolysis in myocardial infarction; TVF, target vessel failure

Study 5 Wilson SJ 2019

Details

Study type	Case series (retrospective study)
Country	UK
Recruitment period	September 2018 to March 2019
Study population and number	n=**54 patients with severely calcified coronary artery lesions treated with IVL during PCI** Indications for PCI non-ST elevation acute coronary syndrome (NSTEACS) in 33.3% (n=18) and STEMI in 18.5% (n=10) of patients, chronic stable angina 46% (n=26), PCI before TAVI (n-1)
Age and sex	Age 71-77 years; 78% (42/54) male
Patient selection criteria	All patients with a clinical indication for revascularisation and had coronary IVL because of non-dilatable coronary artery disease with concentric calcification identified on angiography and or intravascular imaging.
Technique	Patients having PCI (conventional manner) had coronary IVL with the Shockwave Medical system before stent implantation at operator discretion. Pulsatile sonic waves are delivered locally at a rate 1 pulse per second for up to 10 seconds. The process is repeated (up to a maximum of 80 pulses) until the lesion is adequately prepared for stent deployment. At 3 mm from source the energy density is $9.6\pm1.6 \times 10^{-3}$ mJ/mm^2.
Follow up	**Post procedure**
Conflict of interest/source of funding	2 authors received consulting research support and honoraria from Shockwave medical. The cofounder and an employee of the company assisted the authors.

Analysis

Study design issues: retrospective review of all cases done in a single centre; electrophysiological assessment was done, ECG recordings from each patient were reviewed for evidence of induced 'shocktopics' and asynchronous cardiac pacing by 2 cardiologists. ECG recordings were also assessed for evidence of 'shocktopics' triggering atrial or ventricular tachyarrhythmia including non-sustained and sustained VT or VF. Events were recorded by 7 different operators.

Study population issues: the majority of patients were in sinus rhythm (n=44), 7 were in atrial fibrillation, 1 was in atrial flutter and 2 patients had a pacemaker.

Key efficacy and safety findings

Safety

Number of patients analysed: **54**

Adverse events

	% (n)
Death (STEMI complicated by cardiogenic shock in catheter lab)	1
Incidence of ventricular capture (shocktopics and asynchronous cardiac pacing)*	77.8 (42/54)
Atrial pacing	n=3
Shockwave pulses not associated with ventricular capture (sensed but miscounted as an R wave by ECG monitoring)	n=3
Atrial or ventricular tachyarrhythmia due to IVL induced capture	0

*identified as a change in QRS morphology with the onset precisely coinciding with the electromagnetic 'spike' of the shockwave pulse. A shocktopic was defined as an isolated ventricular capture beat. Asynchronous cardiac pacing was defined as more than 2 consecutive ventricular capture beats.

- Compared to patients who did not have ventricular capture, patients in whom this occurred had a lower intrinsic heart rate (61 versus 82 bpm, p<0.001), were more likely to have IVL balloon to the left anterior descending artery (45.2% versus 33.3%), or right coronary artery (42.9% versus 16.7%, p=0.03) and had a shorter QTc interval (424 versus 450 msec, p=0.03).
- Ventricular capture was associated with a fall in systolic blood pressure of between 10 and 35 mmHg that resolved immediately on return of intrinsic rhythm.
- 2 patients who had a pacemaker experienced ventricular capture (but device check revealed no evidence of pacemaker malfunction)

Predictors of ventricular capture

Multivariable logistic regression analysis identified heart rate as the only independent predictor of an increased risk of IVL induced ventricular capture. Patients with a heart rate < 65 bpm before IVL were 16 times more likely (OR 16.3 [2.4-110.8], p=0.004) to experience induced 'shocktopics' compared to patients with a heart ≥ 65.

'Shocktopic' beat morphology was largely uniform in each patient and appeared dependent on the target lesion location.

Abbreviations used: ACS, acute coronary syndrome; bpm, beats per minute; ECG, electrocardiogram; IVL, intravascular lithotripsy; OR, odds ratio; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TAVI, transcatheter aortic valve implantation; VF, ventricular fibrillation; VT, ventricular tachycardia.

Study 6 Wong B 2019

Details

Study type	Case series (retrospective study)
Country	New Zealand
Recruitment period	2018-19
Study population and number	n=**26 patients with severely calcified coronary artery lesions treated with IVL during PCI** Indications for PCI ACS (n=14), stable angina (n=11), PCI before TAVI (n-1)
Age and sex	Mean 72 years; 69% (18/26) male
Patient selection criteria	All patients who had IVL during PCI were sequentially included (including those with acute coronary syndrome and unprotected left main stem intervention).
Technique	Patients having PCI (conventional manner) had coronary IVL before stent implantation at operator discretion. Among patients with ACS, 71% had IVL to the infarct related artery during the index procedure.29% were staged PCIs to severe non-culprit lesions. Upfront IVL was used in 58% of patients, and rest were used after inadequate predilation with balloon angioplasty as a bailout procedure. Different shockwave IVL balloons sizes were used. In 46% patients, after IVL further predilation was done with non-compliant balloons before stent deployment. Lithotripsy done for a maximum of 8, 10 second cycles per device. Each area had minimum 2 cycles of IVL. Mean number of stents used was 1.3. 2 patients needed 6 Fr guide catheter for IVL balloon delivery, and 3 patients needed a buddy wire support technique. 1 patient had an IVL therapy within an old under expanded stent. IVL commonly used in the left anterior descending coronary artery (50%), right coronary artery (35%) and left circumflex artery (12%). In 1 patient, it was used in an unprotected left main stem ostium, in another patient it was used in a patient with inferior ST-elevation myocardial infarction. In 1 patient it was used in multiple vessels (left anterior descending and right coronary artery).
Follow up	**Hospital discharge**
Conflict of interest/source of funding	Study sponsored by Shockwave medical. All authors received fees, grants from different companies. One author is a cofounder of shockwave and 1 had equity in the company, and another is a full-time employee of the company.

Analysis

Follow-up issues: follow up was limited to hospital discharge and no long-term data available.

Study design issues: retrospective study, procedure was not standardised, predilation was used invariably in the study; no intravascular imaging was used systematically in the study; Angiographic success was defined as achieving less than 20% residual stenosis, no edge dissection and thrombolysis in myocardial infarction 3 flow. All complications were recorded. The primary outcome was the ability to deliver the IVL balloon and successful deployment of the stent. Successful clinical outcome was defined as stent delivery without procedural or in-hospital complications (death, MI and target vessel failure).

Study population issues: all target lesions had moderate calcification angiographically. IVL was used in various calcified coronary lesions. There were no angiographic exclusions including length, tortuosity, bifurcation lesions and prior stent placements. Patients had multiple comorbidities.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **26** **Efficacy outcomes** Procedural and clinical success was achieved in all patients. Angiographic success was achieved in all.	**Adverse events** No procedural or in-hospital complications reported.
Abbreviations used: ACS, acute coronary syndrome; IVL, intravascular lithotripsy; MI, myocardial infarction; PCI, percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation	

Validity and generalisability of the studies

- IVL as an adjunct to PCI and stent implantation was evaluated in very few small case series with small sample size and short follow-up period (30 days to 6 months) between 2017 to 2019. The mean age of these patients was 72 years old and 70% of the patients were male. Patients who had treatment had multiple comorbidities.
- Short term clinical data from these studies are promising.
- There are no studies comparing with standard of care.
- There are several case reports that report the experience of IVL as an adjunct to PCI and these have been added to the appendix.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Bioresorbable stent implantation for treating coronary artery disease NICE interventional procedures guidance 492 (2014) Available from http://www.nice.org.uk/guidance IPG492
- Optical coherence tomography to guide percutaneous coronary intervention NICE interventional procedures guidance 481 (2014) Available from http://www.nice.org.uk/guidance IPG481
- Percutaneous laser coronary angioplasty NICE interventional procedures guidance 378 (2011) Available from http://www.nice.org.uk/guidance IPG378
- Intraoperative fluorescence angiography for the evaluation of coronary artery bypass graft patency. NICE interventional procedure guidance 98 (2004) Available from http://www.nice.org.uk/guidance IPG98

Technology appraisals

- Rivaroxaban for preventing major cardiovascular events in people with coronary or peripheral artery disease (ID1397) NICE technology appraisal guidance Publication expected August 2019
- Drug-eluting stents for the treatment of coronary artery disease. NICE technology appraisal guidance 152 (2008) Available from http://www.nice.org.uk/guidance/TA152
- Guidance on the use of coronary artery stents. NICE technology appraisal guidance 71 (2003) replaces TA4 'Ischaemic heart disease coronary artery stents') NICE technology appraisal guidance October 2001 (last modified: July 2008). Available from http://www.nice.org.uk/guidance/TA71

NICE guidelines

- Chest pain of recent onset: assessment and diagnosis NICE guideline 95 (2010, updated 2016) Available from http://www.nice.org.uk/guidance/NG95
- Stable angina. NICE clinical guideline 126 (2011) Available from http://www.nice.org.uk/guidance/NG126
- Unstable angina and NSTEMI. The early management of unstable angina and non-ST-segment-elevation myocardial infarction. NICE clinical guideline 94 (2010) Available from http://www.nice.org.uk/guidance/NG94
- MI – secondary prevention: Secondary prevention in primary and secondary care for patients following a myocardial infarction. NICE clinical guideline 48 (2007) Available from http://www.nice.org.uk/guidance/NG48
- **Medtech guidance**
- HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography (2017) NICE medical technologies guidance 32
- The VeriQ system for assessing graft flow during coronary artery bypass graft surgery. NICE medical technology guidance 8 (2011)
- SeQuent Please balloon catheter for in-stent coronary restenosis. NICE medical technologies guidance 1 (2010)

- **Medtech briefing**
- MIB174: CADScor system for ruling out coronary artery disease in people with symptoms of stable coronary artery disease (2019) NICE medtech innovation briefing 174
- QAngio XA 3D/QFR imaging software for assessing coronary obstructions (2018) NICE medtech innovation briefing 146
- The PressureWire fractional flow reserve measurement system for coronary artery disease (2014) NICE medtech innovation briefing 2
- **Diagnostics guidance**
- New generation cardiac CT scanners (Aquilion ONE, Brilliance iCT, Discovery CT750 HD and Somatom Definition Flash) for cardiac imaging in people with suspected or known coronary artery disease in whom imaging is difficult with earlier generation CT scanners (2012, updated 2017) NICE diagnostics guidance 3

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by specialist advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. 1 specialist adviser questionnaires for intravascular lithotripsy for calcified coronary arteries during percutaneous coronary intervention were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure but 1 patient organisation representing patients who have had

this procedure provided submissions and these were discussed by the committee.

Company engagement

A structured information request was sent to 1 company who manufacture a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

- NCT03595176 Disrupt CAD III with the Shockwave Coronary IVL System. Prospective single-arm study in de novo calcified, stenotic coronary arteries before stenting, n=392, estimated completion date July 2022, status: recruiting. Three sub-studies are included in this protocol; OCT sub-study (n=100), permanent pacemaker and implantable cardioverter defibrillator sub-study (n=20) and hemodynamic sub-study (n=20).
- NCT04151628 Prospective, multicentre, single-arm study of the SWM-1234 in calcified coronary arteries (Disrupt CAD IV Study - Japan) with the Shockwave Coronary C2 IVL system. n=72 patients with de novo, calcified coronary artery lesions presenting with stable or unstable angina and silent ischemia that are suitable for percutaneous coronary intervention assessed for safety and effectiveness of IVL to treat lesions before stenting. status: recruiting, study completion date June 2022.
- Investigator sponsored ongoing research
  - The IVL left main study; a prospective multicentre, non-randomised open pilot study in 50 patients with obstructive calcific distal left main disease (more than 270-degree calcium in at least 1 stenotic segment) and a clinical indication for revascularisation. Study period: 24 months followed up to 12 months, primary end point: efficacy-minimum stent area and residual area stenosis (less than 50%) index immediately post procedure; safety-

composite of major adverse events (all-cause mortality, non-fatal MI or target revascularisation) at 30 days. Location: UK.

- Lithotripsy to aid DCB only PCI, a prospective single arm, single centre study of IVL treatment for DCB only PCI according to criteria on German consensus recommendation on DCB treatment of coronary artery disease. 50 patients with calcific coronary artery lesions of significant severity to warrant interventional therapy and a clinical need for PCI will be included. Study duration 12 months followed up to 4 months. Primary end point - procedural success (defined as DCB or stent delivery with a residual stenosis less than 30% and without in-hospital MACE). Location: Germany.
- The REPLICA clinical trial: Spanish real-world registry of coronary intravascular lithotripsy for the treatment of calcified coronary arteries. Nationwide multicentre prospective observational registry. 400 patients across 30 sites with calcified coronary artery disease requiring PCI with stent implantation will be included. Study duration 24 months followed up to 12 months; primary end point procedural success (defined as the performance of IVL without in-hospital complications, with good angiographic results [TIMI grade 3 and residual stenosis less than 20%]). Location: Spain.
- Balloon angioplasty versus shockwave IVL for calcified coronary stenoses (BASIL study). A prospective single centre randomised (1:1) study. 60 patients with severe coronary calcification as assessed by intravascular ultrasound with presence of more than 270 degrees arc of calcification will be included. Study duration 18 months followed up to 30 days. Primary end point angiographic success (defined as the ability to pre-dilate the target lesion to facilitate stent delivery without bailout techniques or cross over, no intra procedural complications, residual stenosis less than 20% after stent deployment) and clinical success (defined as no procedural related major adverse events and death before discharge). Location: New Zealand.

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2. Ali ZA, Brinton TJ, Hill JM et al. (2017) Optical coherence tomography characterisation of coronary lithoplasty for treatment of calcified lesions: first description. JACC: Cardiovascular Imaging 10(8): 897-906
3. Ali ZA, Nef H, Escaned J (2019) Safety and effectiveness of coronary intravascular lithotripsy for treatment of severely calcified coronary stenoses: The Disrupt CAD II Study. Circulation Cardiovascular Interventions 12(10) :e008434. doi: 10.1161/CIRCINT
4. Aksoy A, Salazar C, Becher MU (2019). Intravascular lithotripsy in calcified coronary lesions: a prospective, observational, multicenter registry. Circulation Cardiovascular Interventions 12(11): e008154. doi: 10.1161/CIRCINTERVENTIONS.119.008154. Epub 2019 Nov 11.
5. Wilson SJ, Spratt JC, Hill J et al. (2019) Coronary intravascular lithotripsy is associated with a high incidence of "shocktopics" and asynchronous cardiac pacing. EuroIntervention pii: EIJ-D-19-00484. doi: 10.4244/EIJ-D-19-00484. [Epub ahead of print]
6. Wong B, El-Jack S, Newcombe R et al. (2019) Shockwave intravascular lithotripsy for calcified coronary lesions: first real-world experience. Journal of Invasive Cardiology 31(3): 46-8

Additional relevant papers

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow up	Direction of conclusions	Reasons for non-inclusion in table 2
Ali Z, McEntegart M, Hill J et al. (2018) Intravascular lithotripsy for treatment of stent underexpansion secondary to severe coronary calcification European Heart Journal 41(3); 14: 485–86	Case report	A 73-year old man with recurrent angina, a high-grade proximal LAD lesion and severe in-stent stenosis (ISS) secondary to stent under expansion had IVL. The outcome was successful.	Larger studies added to table 2.
Costoya IR, Marcos HT, Montilla BV et al. (2019) Coronary lithoplasty: initial experience in coronary calcified lesions. Rev Est Cardio (article in press)	Case report N=3 patients with multivessel coronary artery disease had IVL.	The lithoplasty balloon was successfully used to treat 6 severely calcified lesions. There were no intraprocedural complications such as dissections or perforations.	Larger studies added to table 2.
Curtis E, Khan A, El-Jack A et al. (2019) Precipitation of de novo atrial fibrillation during shockwave intravascular lithotripsy after pacing capture during the treatment of proximal right coronary artery disease: a case report. Euro Heart Journal; doi:10.1093/ehjcr/ytz147	Case report	72-year-old man having planned percutaneous intervention to a heavily calcified proximal right coronary artery (RCA) lesion using S-IVL developed pacing capture from the device and subsequently new atrial fibrillation (AF) during the procedure. The technique resulted in successful treatment of the coronary lesion and he spontaneously reverted within an hour of the procedure before discharge.	Larger studies added to table 2.
Cicovic A, Cicovic S. Wong B et al. (2019) A quicker pace: shockwave lithotripsy pacing with electromechanical capture. JACC CI. 2019: **https://doi.org/10.1016/j.jcin.2019.04.024**	Case report 73 year old woman with calcified lesions in the left anterior ascending artery and right coronary artery had IVL for lesion preparation during PCI.	3 cycles of shockwave therapy given, clear capture of the shockwave spike was captured on ECG, this gave rise to aortic wave forms. The procedure was uneventful with deployment of stents. Patient reported no symptoms and was discharged the next day.	Larger studies included in table.
Dini CS; Tomberli B; Mattesini et al. A (2019) Intravascular lithotripsy for calcific coronary and peripheral artery stenoses. European Society of Cardiology; vol. 15 (no. 8); 714-21	Review	With coronary and peripheral balloons approved in Europe, peripheral balloons approved in the USA and multiple new trials beginning, we review the indications for these recently introduced devices (rotational and orbital atherectomy, IVL), summarise the clinical outcomes	Review

		of the available trials and describe the design of ongoing studies.	
Gonzalez IC, Ferreiro RG, Moreiras JV et al. (2019) Facilitated transfemoral access by shockwave lithoplasty for transcatheter aortic valve replacement. JACC: Cardiovascular Interventions 12(5): e35-8	Case report N=1 patient with severe aortic stenosis, coronary artery disease (CAD) and severe peripheral artery disease had IVL to help transfemoral transcatheter aortic valve replacement.	Results showed a statistically significant reduction in stenosis severity with high acute gain, no major adverse events.	Larger studies added to table 2.
De Silva K, Roy J, Webb I et al. (2019) A calcific, undilatable stenosis; lithoplasty – a new tool in the box? JACC: Cardiovascular Interventions 10(3): 304-6	Case report A 69-year-old man with severe calcific disease in the right coronary artery had PCI after balloon dilation. He had PCI with adjunctive lithotripsy for calcium debulking.	OCT done pre and post lithoplasty showed the calcium 'cracking' effect of the technique. The segment of disease was then treated with a stent with good angiographic result.	Larger studies added to table 2.
Kassimis G, Raina T, Kontogiannis N et al. (2019) How should we treat heavily calcified coronary artery disease in contemporary practice? From atherectomy to intravascular lithotripsy. Cardiovascular Revascularization Medicine. Available January 2019	Review	With the introduction of several adjunctive PCI tools, like cutting and scoring balloons, atherectomy devices, and intravascular lithotripsy technology, the treatment of calcified coronary lesions has become feasible, predictable and safe. This review highlights the techniques in the clinical setting and gives examples of how best to apply them through better patient and lesion selection, with the main objective being optimising drug eluting stent delivery and implantation, and subsequent improved outcomes.	Review
Khan S, Li B, Salata K, et al. (2019) The current status of lithoplasty in vascular calcifications: A systematic review. Surgical Innovation: 1-11	Systematic review N=9 studies 211 patients with vascular calcification lesions had lithoplasty. Follow up: 5.5 months.	Most lesions (72%, 152/212) were in peripheral artery beds, with the remainder occurring in coronary vessels. Lesioned vessels typically had severe calcium burden 62.6% (131/210), with an average initial stenosis of 76.6% (range, 68.1% to 77.8%). After treatment, the average residual stenosis was 21.0% (range, 13.3% to 26.2%), with a mean acute gain of vessel diameter of 2.5 mm. A limited number of type D dissections occurred, with a total of 2.4% (5/211) of patients needing stent implantation. Recent studies	The review included both peripheral and coronary circulation studies. Evidence is from limited quality case series, case reports, and conference abstracts. Peripheral artery disease is out of the

		suggest that lithoplasty is a promising intervention to decrease vessel stenosis in both peripheral artery disease and coronary artery disease, with minimal occurrence of major adverse events. Further research studies, with more rigorous study designs, are needed to determine the effectiveness of lithoplasty in vascular calcifications.	remit of this guidance.
Kwok O-H, Tse, H-F (2019) Ventricular capture during shockwave intravascular lithotripsy JACC: Cardiovascular Interventions; vol. 12 (no. 20); e175-e179	Case report	71-year-old with heavily calcified proximal left anterior descending coronary artery (LAD). Shockwave intravascular lithotripsy (IVL) balloon used for cracking of the calcified lesion. During the 10 s of IVL treatment, there was ventricular capture, mimicking the paced ventricular rhythm. The asynchronous ventricular capture resulted in a transient drop of blood pressure. The patient was asymptomatic. A drug-eluting stent was implanted, which was further expanded by noncompliant balloons under OCT guidance. Final angiogram and OCT run showed an excellent result.	Larger studies included in table 2.
Legutko J, Niewiera L, Tomala M et al. (2019) Successful shockwave intravascular lithotripsy for severely calcified undilatable lesion of the left anterior descending coronary artery in patient with recurrent myocardial infarction. Kardiologia Poloska (published online June 6)	Case report N=1 patient with severely calcified, critical narrowing of left anterior descending coronary artery associated with a history of recurrent myocardial infarction had IVL	Angiography, intravascular ultrasound and OCT confirmed optimal PCI result with perfect stent expansion and apposition. No complications occurred during hospitalisation and patient was discharged home 48 hours after the procedure free of angina and ventricular arrhythmia.	Larger studies included in table 2.
Luigi De Maria G, Scarsini R, Banning A (2019) Management of calcific coronary artery lesions: Is it time to change our interventional therapeutic approach? JACC: Cardiovascular Interventions 12 (15), 1465-78	Review	This review provides an overview about coronary lesions with a high calcium content with special focus on existing and emergent technologies. We also provide a proposed procedural algorithm to facilitate optimal use of technology according to specific features of LHCC and coronary anatomy.	Review
Mathias B, Federico M, Stefan T et al. (2019) The effect of lithoplasty on coronary arteries. Cardiovascular medicine 22:02013	Case report 79-year-old man with non-ST-elevation myocardial infarction and a heavily calcified bifurcation stenosis of	The subsequent OCT showed calcium containing cracks in the intima and the media of the LAD. The bifurcation lesion was treated with 2 stents. The final OCT	Larger studies included in table 2.

	the left anterior descending artery (LAD) had IVL	showed good stent expansion and apposition.	
Morabito G, Tripolino Cesare, Tassone EJ (2018). A case of stent under-expansion due to calcified plaque treated with shockwave lithoplasty. Cardiology; 2018; vol. 141 (no. 2); 75-7	Case report Stent under-expansion due to heavily calcified plaque treated with the shockwave lithoplasty system.	A 77-year-old woman had coronary angiography, and intravascular ultrasound revealed stent under-expansion due to calcified plaque. Shockwave lithoplasty balloon was used to disrupt calcium deposits around the stent, thereby allowing a correct stent expansion with an excellent angiographic and intravascular ultrasound result.	Larger studies included in table 2.
Sgueglia GA, Gioffre G, Piccioni F et al. (2019) Slender distal radial five French coronary shockwave lithotripsy. Catheter cardiovascular Interventions 1-4	Case report 72-year-old man with calcific atherosclerosis of the left anterior descending artery with stenosis had IVL PCI using a 5 French guiding catheter.	Procedure was successful with optimal stenting results and reported no complications at 6 months follow up.	Larger studies added to table 2.
Shavadia JS, Minh NV, Kevi B. (2018) Challenges with severe coronary artery calcification in percutaneous coronary intervention: A Narrative Review of Therapeutic Options. Canadian Journal of Cardiology, 3 (12): 156-72	Review	Summary of the principles, technique, and contemporary evidence for the currently approved devices designed to treat severe coronary calcific lesions.	Review
Salazar C, Escaned J, Tirado G et al. (2019) Undilatable calcific coronary stenosis causing stent under expansion and late stent thrombosis. A complex scenario successfully managed with intravascular lithotripsy. JACC: Cardiovascular Interventions. 12(15): 1510-3	Case report N=71-year-old man with repeat STEMI had PCI. A suboptimal under expansion was achieved by coronary calcification. A new PCI using IVL was done to modify calcific plaques.	A good final angiography result was achieved. The case showed effectiveness of IVL to modify calcific plaques and act through a previously implanted stent.	Larger studies added to table 2.
Soriano, F, Veas, N. Piccinelli, E et al. Coronary dissection due to Intravascular lithoplasty balloon rupture. EuroIntervention. 2019; DOI: 10.4244/EIJ-D 19-00383	Case report of a 47 year old man with heavily calcified left anterior descending stenosis in a tortuous anatomy. Patient had PCI using OCT and IVL.	IVL was done with a balloon at 4atm. At the second delivery phase, the IVL balloon broke with subsequent dissection of the LAD. Finally 2 stents were delivered and post dilation was done.	Larger studies added to table 2.

Tomasiewicz, B.; Kosowski, M.; Zimoch, W. Heavily calcified coronary lesion treated by shockwave intravascular lithotripsy. Kardiologia Polska; 2019; vol. 77 (no. 9); 890-1	Case report -heavily calcified coronary lesion in the proximal left anterior descending artery treated with shockwave lithotripsy	This case shows that complex, heavily calcified coronary lesions always require a thoughtful approach, and often more than 1 plaque modification technique should be considered. Intra-vascular lithotripsy using the Shockwave device proved efficient and safe.	Larger studies included in table 2.
Tassone EJ, Tripolino C, Morabito G et al. (2018) When calcium gets tough, the tough cardiologist starts to play. Cardiology, 141: 167-71	Case report N=60-year-old man with calcific restenosis of a previously stented or treated lesion (left coronary artery) had coronary shockwave lithotripsy.	IVUS after 3 cycles showed a statistically significant area gain more than 6 mm^2. There was an excellent postprocedure angiographic result and a minimal lumen area on final IVUS. The patient was discharged after 48 hours in good condition and without symptoms.	Larger studies added to table 2.
Tovar Forero, MN, Wilschut J, Van Mieghem NM et al. (2019) Coronary lithoplasty: a novel treatment for stent under expansion. European Heart Journal. 40, 2: 221	Case report N= 74-year-old man with a heavily calcified stenotic lesion in the proximal left anterior descending coronary artery and under expanded stent resistant to conventional non-compliant balloons had coronary shockwave lithotripsy.	Full expansion was achieved after 2 lithoplasty therapies. OCT imaging showed multiple calcium fractures. The procedure completed without any complications.	Larger studies added to table 2.
Tripolino C, Tassone EJ, Morabito G (2019) ST-elevation myocardial infarction due to stent underexpansion managed with coronary lithoplasty. Reviews on recent clinical trial; Volume 14, Issue 4, DOI : 10.2174/1574887114666190927164253	Case report	An 80-year-old Caucasian man with ST elevation myocardial infarction had emergent coronary angiography showing complete intrastent thrombosis at the proximal trait of LAD. After thrombus removal, it was evident stent under-expansion at its proximal edge caused by vascular calcification. Coronary shockwave lithoplasty was chosen to treat this lesion. After calcium deposits disruption we were able to obtain complete stent expansion. This demonstrates the usefulness and safety of the lithoplasty system in the context of ST elevation myocardial infarction.	Larger studies included in table 2
Tripolino C, Tassone E.J, Morabito G (2019) Intravascular ultrasound-guided shockwave treatment of stents overlapping under expansion of calcified left	Case report	A 65-year-old man with angina, had coronary angiography and intravascular ultrasound showing restenosis, in a site of overlapping stents, due to calcified tissue. Shockwave lithoplasty balloon was able to	Larger studies included in table 2

anterior descending artery. Journal of Cardiology Cases; vol. 20 (no. 4); 135-7		break calcified tissue in a site of overlapping stents, allowing subsequent vessel dilation and repeat stent implantation with optimal final stent expansion.	
Vainer J, Lux A, Ilhan M et al. (2019) Smart solution for hard times: successful lithoplasty of an undilatable lesion. Neth Heart J 27:216-7	Case report N=70-year-old woman with unsuccessful PCI with high-pressure balloons and rotational atherectomy had lithoplasty-assisted PCI.	Lithoplasty effectively resulted in plaque modification and a statistically significant increase in diameter. OCT showed typical calcium tears and a large dissection. To cover the lesion, a drug-eluting stent was implanted. Proper stent expansion and apposition were confirmed with OCT.	Larger studies added to table 2.
Venuti G, D'Agosta G, Tamburino C et al. (2019). Coronary lithotripsy for failed rotational atherectomy, cutting balloon, scoring balloon and ultra-high-pressure non-compliant balloon. Catheter Cardiovascular Interventions 1-5	Case report N= 67-year-old man having planned PCI of the right coronary artery targeting an undilatable lesion already resistant to multiple specialised balloons and rotational atherectomy had coronary lithotripsy and new PCI on the RCA.	Calcium modification at the target segment was seen and 3 stents were deployed with a good final result. No intra hospital complications reported. Patient was free from angina at 3 months follow up.	Larger studies added to table 2.
Watkins, S, Good, R, Hill J, et al. (2018) Intravascular lithotripsy to treat a severely under-expanded coronary stent. EuroIntervention.; Jaa-457 DOI: 10.4244/EIJ-D-18-00780.	Case report 67 year old with occluded left anterior descending artery, right coronary artery stenosis, and under expansion of proximal lesion following PCI had IVL to facilitate full stent expansion.	The outcome was successful and effects were immediate and near complete stent expansion during the first cycle of energy.	Larger studies included in table 2.
Warisawa, T, Goto, S, Salazar, C et al. (2019) Safety and feasibility of coronary lithotripsy supported by guide extension catheter for the treatment of calcified lesion in angulated vessel. CRM.; **https://doi.org/10.1016/j.carrev.2019.02.014**	Case report	A case of successful coronary intervention with coronary lithotripsy facilitated by guide extension catheter for the treatment of severely calcified and bent vessel. The guide extension catheter accommodated it with ease and helped smooth delivery of it. This shows the usefulness of this device combination for patients with complex coronary anatomies.	Larger studies added to table 2.
Wong B, El -Jack S et al. (2019) Shockwave intravascular lithotripsy of calcified coronary lesions in ST-elevation	Case series N=3 patients having PCI for ST-elevation myocardial	The 3 presented cases include an upfront use of S-IVL in a right coronary artery, an in-stent restenosis, and a community cardiac arrest/ST-elevated	Larger studies added to table 2. (cases also reported in

myocardial infarction: first in-man experience. Journal of invasive cardiology 31 (5), e73-5	infarction (STEMI) using IVL as an adjunct procedure.	myocardial infarction equivalent when S-IVL was used as a bailout technique to help stent delivery in a tortuous calcified vessel. Early experience has been favourable.	study 3 in table 2)
Wong B, El -Jack S, Khan S et al. (2019) Treatment of heavily calcified unprotected left main disease with lithotripsy-the first case series. The journal of invasive cardiology, 31 (6): E143-7	Case series N=3 the use of S-IVL in a patient with left main-coronary artery disease (LM-CAD) with multivessel disease who declined surgery, a patient with an isolated LM-CAD and severe cardiomyopathy, and a late nonagenarian patient when surgical revascularisation was not an option reported.	No patients had procedural complications or major adverse events (stroke, myocardial infraction, death) during the index admission or within the first 30 days post discharge.	Larger studies included in table 2
Yeoh J, Hill J, Spratt JC et al. (2019) Intravascular lithotripsy assisted chronic total occlusion revascularization with reverse controlled antegrade retrograde tracking. Catheter Cardiovasc Interv, 93:1295-7	Case report 81-year-old female with heavily calcified right coronary artery chronic total occlusion (CTO) had PCI via reverse controlled antegrade/retrograde tracking (R-CART).Standard balloon inflation failed to create communication by modifying plaque and guidewire failed. So IVL was used in controlled antegrade/retrograde tracking.	IVL was used to help connection in R-CART to complete the CTO PCI when heavy calcification was present at the site of chronic occlusion. Multiple fractures helped connection between intimal and subintimal tissue planes.	Larger studies added to table 2.
Yeoh, J.; Hill, J (2019) Intracoronary lithotripsy for the treatment of calcified plaque. Interventional Cardiology Clinics; vol. 8 (no. 4); 411-24	Review	This article reviews intravascular lithotripsy technology, the evidence in the literature, and the advantages and disadvantages compared with other forms of calcium modification and discusses its role in specific subsets of coronary lesions. It concludes with a discussion about the future direction of research involving this new technology as its role within percutaneous cardiac procedures becomes more defined.	Review

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	18/11/19	Issue 11 of 12, November 2019
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	18/11/19	Issue 11 of 12, November 2019
HTA database (CRD website)	18/11/19	-
MEDLINE (Ovid)	13/11/19	1946 to November 12, 2019
MEDLINE In-Process (Ovid) & Medline ePub ahead (Ovid)	13/11/19	1946 to November 12, 2019
EMBASE (Ovid)	13/11/19	1974 to 2019 November 12

Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

MEDLINE search strategy

The MEDLINE search strategy was adapted for use in the other sources.

1 Coronary Artery Disease/ (59160)
2 Acute Coronary Syndrome/ (14603)
3 Myocardial Infarction/ (162853)
4 exp Angina Pectoris/ (42991)
5 Myocardial Ischemia/ (37984)
6 Vascular Calcification/ (3839)
7 Plaque, Atherosclerotic/ (8358)

8 Coronary Stenosis/ (11324)
9 ((coronar* or isch?em*) adj4 (arter* or heart* or vasc*) adj4 (diseas* or disord* or lesion* or stenos* or calcium*)).tw. (159973)
10 (coronar* adj4 (arterioscleros* or atheroscleros*)).tw. (11361)
11 ((Myocardial* or heart*) adj4 (infarct* or isch?emia* or stenos*)).tw. (203190)
12 (heart adj4 attack*).tw. (5058)
13 (acute* adj4 coronar* adj4 syndrome*).tw. (25324)
14 angina*.tw. (49873)
15 (calcif* adj4 (coronar* or heart* or vasc*) adj4 (lesion* or stenon* or arter* or plaque*)).tw. (3544)
16 (vascular* adj4 (calcific* or calcinos*)).tw. (4292)
17 atheroma*.tw. (9995)
18 fibroatheroma*.tw. (571)
19 (atheroscler* adj4 plaque*).tw. (15619)
20 (arterial adj4 fat* adj4 streak*).tw. (21)
21 (CHD or CAD or MI or ACS or PCI).tw. (119335
22 Percutaneous Coronary Intervention/ (15980)
23 (percutan* adj4 coronar* adj4 intervention*).tw. (26552)
24 PCI.tw. (20069)
25 or/1-24 (520441)
26 Lithotripsy/ (9643)
27 (lithotrip* or litholapax* or lithoplast*).tw. (9772)
28 shockwave*.tw. (2177)
29 (IVL or S-IVL).tw. (395)
30 (calcif* and (plaque* adj4 modif*)).tw. (73)
31 or/26-30 (13311)
32 25 and 31 (156)
33 animals/ not humans/ (4609130)
34 32 not 33 (148)
35 limit 34 to english language (136)
36 limit 35 to ed=20190601-20191130 (16)

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Cardiovascular Revascularization Medicine

Efficacy and Safety of Intravascular Lithotripsy in Calcified Coronary Lesions: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Intravascular lithotripsy (IVL) is a recently introduced therapeutic modality in the management of calcified coronary lesions (CCAD). IVL delivers sonic pressure waves to modulate calcium, hence promote vessel compliance and optimize stent deployment.
Methods: We performed a comprehensive literature search for studies that evaluated the utility of adjunctive IVL. The primary outcomes of our study were the clinical success, defined as the ability of IVL to produce residual diameter stenosis <50% (RDS < 50%) after stenting with no evidence of in-hospital major adverse cardiac events, and the angiographic success, defined as success in facilitating stent delivery with RDS < 50% and without serious angiographic complications. The secondary outcomes included post-IVL and post-stenting changes in lumen area, calcium angle, and the maximum calcium thickness. Proportional analysis was used for binary data and mean difference was used for continuous data. All meta-analyses were conducted using a random-effect model and 95% confidence intervals (CIs) were included.
Results: A total of eight single-arm observational studies, including 980 patients (1011 lesions), were included. 48.8% of the patients presented with acute coronary syndrome. Severe calcifications were present in 97% of lesions. Clinical success was achieved in 95.4% of patients (95%CI:92.9%–97.9%). Angiographic success was achieved in 97% of patients (95%CI:95%–99%). There was an overall increase in postprocedural lumen area as well as significant reduction of calcium angle and maximum calcium thickness.
Conclusions: IVL seems to have excellent efficacy and safety in the management of CCAD. However, adequately powered RCTs are needed to evaluate IVL compared to other calcium/plaque modifying techniques.

1. Introduction

Calcified coronary lesions (CCL) are not uncommon and frequently observed during coronary angiography, with a reported prevalence ranging between 18% and 26% [1]. The incidence of CCL increases with age and other cardiovascular risk factors, particularly diabetes mellitus (DM), hypertension, and renal dysfunction [2]. Coronary artery calcification (CAC) is associated with increased arterial stiffness and highly correlates to the rate of cardiac adverse events [3]. The presence of CCL renders them resistant to conventional intervention making percutaneous coronary intervention (PCI) procedures more challenging, with substantial failure to gain satisfactory artery expansion and higher risks of dissection, perforation, and re-stenosis [4].

Several specialty balloons such as high-pressure non-compliant, scoring, and cutting balloons have been developed to modify the calcific plaque thereby promoting effective vessel dilatation and therefore enhance stent deployment [5]. However, these balloons are often associated with limited calcium debulking efficacy due to the eccentric nature of calcification. The more effective rotational and orbital atherectomy are even associated with inhomogeneous ablation leaving substantial areas of unmodified calcium plaques, particularly in eccentric lesion [6]. Furthermore, these modalities are often associated with increased risk of periprocedural complications including slow or no-flow, coronary dissection, or perforation, which occur more frequently with atherectomy techniques as compared to balloon techniques [5].

Intravascular lithotripsy (IVL) is a recently introduced therapeutic modality in managing CCL to overcome limitations of the more commonly applied practices with non-compliant or cutting balloons or rotational atherectomy. IVL promotes vessel compliance and optimizes

Abbreviations: ACS, acute coronary syndrome; CAC, coronary artery calcification; CAD, coronary artery disease; CCAD, calcified coronary artery disease; CCL, calcified coronary lesions; DES, drug-eluting stent; IVL, intravascular lithotripsy; MACE, major adverse cardiac events; MLA, minimal luminal area; MLD, minimal luminal diameter; MSA, minimal stent area; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; RDS, residual diameter stenosis.

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META ANALYSIS AND SYSTEMATIC REVIEW

Systematic review: Accuracy of the enhanced liver fibrosis test for diagnosing advanced liver fibrosis and cirrhosis

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Declaration of conflict of interest: WMR has received sponsorship from Gilead Sciences to attend meetings and has served on advisory boards for Gilead Sciences. WMR is an inventor of the ELF test and has received speaker's fees from Siemens Healthineers.
Author contribution: C. S. performed the research. C. S., S. C., and N. E. collected and analyzed the data. C. S., S. C., and N. E. designed the research study and wrote the paper. W. M. R. and J. P. supervised C. S., S. C., and N. E., reviewed the paper, and made final critical revision for important intellectual contents. All authors have approved the final version of this manuscript.
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Abstract

Background and Aims: The rising incidence of chronic liver disease (CLD) has increased the need for early recognition. This systematic review assesses the diagnostic accuracy of the enhanced liver fibrosis (ELF) test in cases of advanced fibrosis and cirrhosis due to multiple etiologies in at-risk populations.
Methods: Studies evaluating the ELF accuracy in identifying advanced fibrosis or cirrhosis, defined as METAVIR stage $F \geq 3$ and $F = 4$ or equivalent, in patients with non-alcoholic fatty liver disease (NAFLD), alcohol liver disease (ALD), or viral hepatitis were included. Liver biopsy was used as the reference standard. Medline and Embase databases were searched. The QUADAS-2 tool was used as a framework to assess risk of bias and applicability. The area under the receiver operator curve (AUROC) was extracted as a summary measure of diagnostic accuracy.
Results: Thirty-six studies were included: 11 hepatitis C, 4 hepatitis B, 9 NAFLD, 2 ALD, and 10 mixed. The ELF test showed good diagnostic performance in detecting advanced fibrosis in patients with viral hepatitis (AUROC 0.69 to 0.98) and excellent performance in NAFLD (AUROC 0.78 to 0.97) and ALD (AUROC from 0.92 to 0.94). There is also evidence of good diagnostic performance for detecting cirrhosis in patients with viral hepatitis (AUROC 0.63 to 0.99), good performance in NAFLD (AUROC 0.85 to 0.92), and excellent performance in patients with ALD (AUROC 0.93 to 0.94).
Conclusion: This systematic review supports the use of the ELF test across a range of CLD as a possible alternative to liver biopsy in selected cases.

Background

Target condition. Chronic liver disease (CLD) is a leading cause of death globally, with liver-related deaths increasing in England compared with other major killers.[1] The commonest causes of CLD are alcohol, obesity, and viral hepatitis. CLD can lead to liver fibrosis characterized by increased synthesis and altered deposition of extracellular matrix. Fibrosis is usually silent until cirrhosis leads to complications of portal hypertension including variceal bleeding, ascites, and hepatocellular carcinoma. Many patients with CLD present when it is too late to prevent these complications, and they can only be ameliorated. There is a need for tests to detect the presence of fibrosis before it causes irreversible damage, to stratify which patients might benefit from specialist care, and to target surveillance for complications.[2]

Liver biopsy is the reference test for assessing liver fibrosis, but its accuracy is limited by sampling error and inter-observer and intra-observer variation.[3,4] Additionally, it is invasive and can

Circulation

ACC/AHA/SCAI CLINICAL PRACTICE GUIDELINE

2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

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AIM: The guideline for coronary artery revascularization replaces the 2011 coronary artery bypass graft surgery and the 2011 and 2015 percutaneous coronary intervention guidelines, providing a patient-centric approach to guide clinicians in the treatment of patients with significant coronary artery disease undergoing coronary revascularization as well as the supporting documentation to encourage their use.

METHODS: A comprehensive literature search was conducted from May 2019 to September 2019, encompassing studies, reviews, and other evidence conducted on human subjects that were published in English from PubMed, EMBASE, the Cochrane Collaboration, CINHL Complete, and other relevant databases. Additional relevant studies, published through May 2021, were also considered.

STRUCTURE: Coronary artery disease remains a leading cause of morbidity and mortality globally. Coronary revascularization is an important therapeutic option when managing patients with coronary artery disease. The 2021 coronary artery revascularization guideline provides recommendations based on contemporary evidence for the treatment of these patients. The recommendations present an evidence-based approach to managing patients with coronary artery disease who are being considered for coronary revascularization, with the intent to improve quality of care and align with patients' interests.

Key Words: AHA Scientific Statements ■ percutaneous coronary intervention ■ angioplasty ■ coronary artery bypass graft surgery ■ myocardial infarction ■ cardiac surgery, stent(s) ■ angiogram ■ angiography ■ percutaneous transluminal coronary angioplasty ■ coronary atherosclerosis ■ saphenous vein graft ■ internal mammary artery graft ■ internal thoracic artery graft ■ arterial graft ■ post-bypass ■ non–ST-segment–elevated myocardial infarction ■ vein graft lesions ■ myocardial revascularization ■ multivessel PCI ■ left ventricular dysfunction

*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry may apply; see Appendix 1 for detailed information. †ACC/AHA Representative. ‡ACC/AHA Joint Committee on Clinical Practice Guidelines Liaison. §ACC/AHA Task Force on Data Standards Representative. ‖SCAI Representative.

ACC/AHA Joint Committee on Clinical Practice Guidelines Members, see page e80.

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National Institute for Health and Care Excellence

Final version

Non-alcoholic fatty liver disease

Assessment and management

NICE guideline NG49

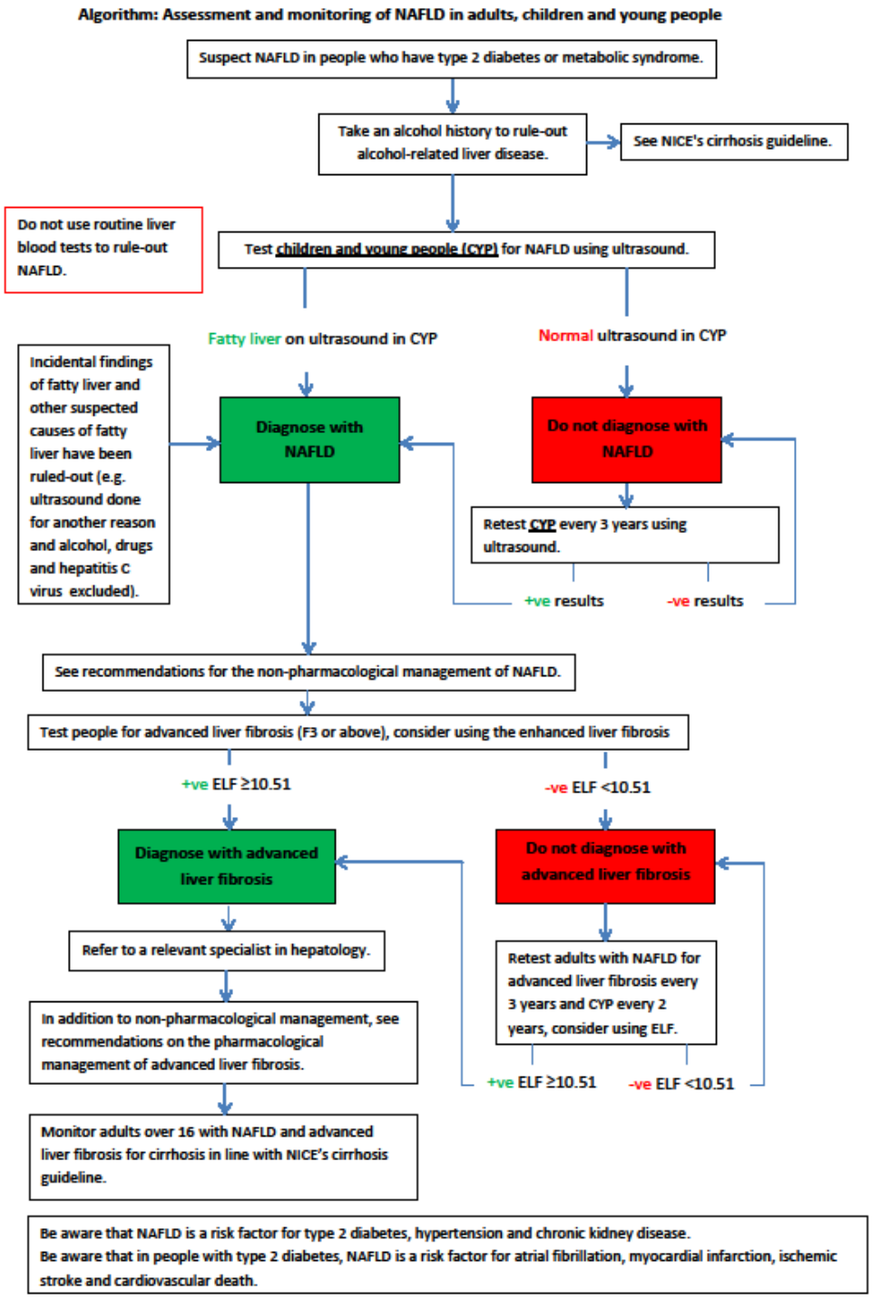
Methods, evidence and recommendations

July 2016

Developed by the National Guideline Centre,
hosted by the Royal College of Physicians

1 Guideline summary

1.1 Algorithm: Assessment and monitoring of NAFLD in adults, children and young people



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Clinical Practice Guidelines

American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings

Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD)

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ABSTRACT

Objective: To provide evidence-based recommendations regarding the diagnosis and management of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) to endocrinologists, primary care clinicians, health care professionals, and other stakeholders.
Methods: The American Association of Clinical Endocrinology conducted literature searches for relevant articles published from January 1, 2010, to November 15, 2021. A task force of medical experts developed evidence-based guideline recommendations based on a review of clinical evidence, expertise, and informal consensus, according to established American Association of Clinical Endocrinology protocol for guideline development.

NAFLD Algorithm Task Force: Kenneth Cusi, MD, FACE, FACP, Co-Chair; Scott Isaacs, MD, FACE, FACP, Co-Chair; Diana Barb, MD, ECNU; Sonia Caprio, MD; Sangeeta Kashyap, MD; Karl Nadolsky, DO, FACE, DABOM.

Disclaimer: The American Association of Clinical Endocrinology clinical practice guidelines include systematically developed recommendations to assist health care professionals in medical decision-making for specific clinical conditions. Most of the content herein is based on scientific evidence. In areas of uncertainty, or when clarification is required, expert opinion and professional judgement were applied.

This guideline is a working document that reflects the state of the field at the time of publication. Since rapid changes in this area are expected, periodic revisions are inevitable. We encourage health care professionals to use this information in conjunction with their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision(s) by health care professionals to apply the recommendations provided in this guideline must be made in consideration of local resources and individual patient circumstances.

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steatohepatitis
weight loss
GLP-1 RA
pioglitazone

Recommendation Summary: This guideline includes 34 evidence-based clinical practice recommendations for the diagnosis and management of persons with NAFLD and/or NASH and contains 385 citations that inform the evidence base.

Conclusion: NAFLD is a major public health problem that will only worsen in the future, as it is closely linked to the epidemics of obesity and type 2 diabetes mellitus. Given this link, endocrinologists and primary care physicians are in an ideal position to identify persons at risk on to prevent the development of cirrhosis and comorbidities. While no U.S. Food and Drug Administration-approved medications to treat NAFLD are currently available, management can include lifestyle changes that promote an energy deficit leading to weight loss; consideration of weight loss medications, particularly glucagon-like peptide-1 receptor agonists; and bariatric surgery, for persons who have obesity, as well as some diabetes medications, such as pioglitazone and glucagon-like peptide-1 receptor agonists, for those with type 2 diabetes mellitus and NASH. Management should also promote cardiometabolic health and reduce the increased cardiovascular risk associated with this complex disease.

Lay Abstract

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease affecting 25% of the global population. Despite the sizable and growing prevalence, disease awareness remains limited with <5% of persons with NAFLD being aware of their disease compared with 38% of persons with viral hepatitis. Twelve to 14% of persons with NAFLD have a more aggressive form known as nonalcoholic steatohepatitis (NASH), which can progress to advanced liver fibrosis, cirrhosis, or liver cancer. The risk of NASH is two- to threefold higher in persons with obesity and/or type 2 diabetes mellitus. NASH is among the top causes of liver cancer and the second most common indication for liver transplantation in the United States after hepatitis C. NAFLD is diagnosed by abnormal liver test results (although liver test results may be normal) and imaging studies, not related to excess alcohol use or other causes of liver disease. NASH is diagnosed by a liver biopsy; however, specialized blood tests and imaging can determine the risk of significant fibrosis. NAFLD is associated with cardiometabolic disorders: (1) obesity, (2) insulin resistance, (3) type 2 diabetes mellitus, (4) high blood pressure, and (5) atherogenic dyslipidemia, all of which increase the risk of a heart attack or stroke, the most common cause of death. The primary treatment of NAFLD is weight loss with a low-calorie diet; restriction of saturated fat, starch, and sugar; improved eating patterns (eg, Mediterranean diet and minimally processed whole foods); and exercise. Cardiometabolic benefit and reduction of liver fat can be observed with >5% weight loss. More weight loss provides increased benefits and may reverse steatohepatitis or liver fibrosis (≥10% weight loss). There are no U.S. Food and Drug Administration-approved medications for the treatment of NAFLD; however, some diabetes and antiobesity medications can be beneficial. Bariatric surgery is also effective for weight loss and reducing liver fat in persons with severe obesity.

Abbreviations

AACE, American Association of Clinical Endocrinology; AASLD, American Association for the Study of Liver Diseases; ABCD, adiposity-based chronic disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; aHR, adjusted hazard ratio; BEL, best evidence level; BMI, body mass index; CAP, controlled attenuation parameter; CI, confidence interval; CKD, chronic kidney disease; CMD, cardiometabolic disease; CPG, Clinical Practice Guidelines; CV, cardiovascular; CVD, cardiovascular disease; EBMT, Endoscopic bariatric and metabolic therapy; ELF, enhanced liver fibrosis; ESG, endoscopic sleeve gastroplasty; FDA, U.S. Food and Drug Administration; FIB-4, fibrosis-4 index; GH, growth hormone; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HCC, hepatocellular carcinoma; HR, hazard ratio; ^{1}H-MRS, proton magnetic resonance spectroscopy; IGB, intragastric balloon; IHTG, intrahepatic triglyceride; IR, insulin resistance; LSM, liver stiffness measurement; MACE, major adverse cardiovascular event; MetS, metabolic syndrome; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; NFS, NAFLD fibrosis score; NPV, negative predictive value; OR, odds ratio; PCOS, polycystic ovary syndrome; PCP, primary care physician; PNPLA3, patatin-like phospholipase domain-containing 3; PPAR, peroxisome proliferator-activated receptor; PPV, positive predictive value; pSWE, point shear wave elastography; RCT, randomized controlled trial; RYGB, Roux-en-Y gastric bypass; SGLT2, sodium-glucose cotransporter 2; SWE, shear wave elastography; TBW, total body weight; TE, transient elastography; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus; US, ultrasonography; 2DSWE, 2-dimensional shear wave elastography; VCTE, vibration-controlled transient elastography.

Structure of Clinical Practice Guideline

1. Introduction
   - Epidemiology of Adult and Pediatric NAFLD
   - Purpose
   - Scope
   - Limitations of the Literature
2. Methods
3. Summary of Recommendations: summary list of all recommendations developed for this clinical practice guideline
4. Recommendations With Evidence Base
   - Recommendation
   - Recommendation Grade, Strength of Evidence Grade, and Best Evidence Level
   - Evidence Base: summary of clinical background and highlighted studies that best support the recommendation

Introduction

Epidemiology

What Is the Magnitude of the Problem/Disease Burden in Endocrine and Primary Care Clinics?

Nonalcoholic fatty liver disease (NAFLD) is part of a multisystemic disease and is closely associated with obesity, insulin resistance (IR), type 2 diabetes mellitus (T2D), hypertension, and atherogenic dyslipidemia.[1,2] The definition of NAFLD is based on the presence of hepatic steatosis in >5% of hepatocytes in the absence of significant ongoing or recent alcohol consumption and other known causes of liver disease.[1,2] Nonalcoholic steatohepatitis (NASH), more likely to progress to advanced stages of fibrosis, is characterized by the presence of active hepatocyte injury (ballooning) and inflammation in addition to steatosis (Table 1 shows the common terms and definitions, and Table 2 shows the histologic definition of NAFLD grades and fibrosis stages).

2023 CPT Code Review
HIPEC

Plain Language Summary:

Coverage question: Should OHP cover a treatment for certain types of advanced cancer? Doctors heat up a special chemotherapy medicine and put it directly into the abdomen (peritoneum) to treat cancer that might be there. The heat and the medicine together can help fight the cancer.

Should OHP cover this treatment? Yes, the advantages of treatment are greater than the potential harms for certain advanced cancers.

Codes:
96547 Intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) procedure, including separate incision(s) and closure, when performed; first 60 minutes (List separately in addition to code for primary procedure)
96548 each additional 30 minutes

Information: Peritoneal carcinomatosis is an advanced form of cancer resulting from the spread of gastrointestinal, gynecological and other malignancies throughout the abdomen. Cytoreduction surgery is done to remove all macroscopic tumors within the abdominal cavity. At the time of cytoreduction surgery, hyperthermic intraperitoneal chemotherapy (HIPEC) can be done. HIPEC is a technique in which chemotherapy is delivered in a heated solution perfused throughout the peritoneal space. The rationale for hyperthermic delivery is that heat can increase penetration of the chemotherapy at the peritoneal surface and enhance the sensitivity of cancer cells to chemotherapy by inhibiting DNA repair.

Evidence
NICE 2021, evidence review of cytoreduction surgery (CRS) with hyperthermic intraoperative peritoneal chemotherapy (HIPEC) for peritoneal carcinomatosis

1) Peritoneal carcinomatosis from ovarian and endometrial cancers
    1. A systematic review of 1,168 patients (in 16 studies) with recurrent ovarian cancer having cytoreduction surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) reported that overall survival ranged between 26.7 and 30 months. Median overall survival across 6 studies ranged from 25.7 to 45.7 months. A randomized controlled trial (RCT) (Spiliotis 2015) included in the systematic review reported that overall mean survival in the CRS and HIPEC group was significantly longer than for CRS and chemotherapy (26.7 months compared with 13.4 months, p=0.006). An RCT of 245 patients comparing CRS plus HIPEC (n=123) with CRS alone (n=122) for treatment of advanced ovarian cancer reported that CRS plus HIPEC resulted in longer median overall survival by 11.8 months than CRS alone (CRS plus HIPEC group 45.7 months compared with CRS alone 33.9 months). A meta-analysis of 1,608 patients from 26 studies on CRS

and HIPEC in patients with advanced epithelial ovarian cancer (n=534) and recurrent ovarian cancer (n=1,074) reported a median overall survival of 63 months in advanced cancer and 39 months in recurrent cancer. In a systematic review and meta-analysis of 13 studies of HIPEC and CRS for patients with ovarian cancer, a pooled analysis of 12 studies showed a significant improvement in overall survival for patients who had HIPEC, compared with patients who had CRS (HR 0.56, 95% CI 0.41 to 0.76, p<0.01).

2) Peritoneal carcinomatosis from gastric cancer
    1. A systematic review and meta-analysis of 620 patients (14 studies) with peritoneal carcinomatosis from gastric cancer who had CRS and HIPEC reported that the overall survival rate was higher, but not statistically significant, for the CRS and HIPEC group compared with the control group at 1-year follow up (risk ratio [RR]=0.67, 95% CI 0.52 to 0.86), 2-year follow up (RR=0.87, 95% CI 0.73 to 1.04, p=0.12) and 3-year follow-up (RR=0.99, 95% CI 0.93 to 1.06, p=0.85)
3) Peritoneal carcinomatosis from colorectal cancer
    1. A systematic review and meta-analysis of 10,036 patients (in 76 studies including 15 controlled and 61 non-controlled studies) who had treatments for peritoneal carcinomatosis from colorectal cancer reported that the mean overall survival rate for CRS plus HIPEC was 29.2 (±11.3) months. Meta-analysis of 15 controlled studies (including 3,179 patients) reported that the mean overall survival for the CRS plus HIPEC treatment group was 34.3 (±14.8) months and the traditional therapy group was 18.8 (±8.8) months. The summarized hazard ratio for overall survival was 2.67 (95% CI 2.21 to 3.23, I2=0%, p <0.00001).
4) Safety
    1. Systematic reviews and meta-analysis of HIPEC for gynecologic cancer found a perioperative mortality rate of 1-5%, for gastric cancer found perioperative mortality rate of 0-7%, and for colorectal cancer the perioperative mortality rate was 3%
    2. The systematic review of 13 studies of people with ovarian cancer reported an overall postoperative morbidity rate of 20% to 30%. The most frequent events were bone marrow depression, gastrointestinal fistulation, anemia, renal failure or acute kidney injury. Other adverse events included pleural effusion, post-operative bleeding, abdominal abscess, urinary tract infection, leucopenia, thrombocytopenia, neutropenia, lymphocyst needing drainage, infected central catheter, transient hematological toxicity, transient confusional syndrome, prolonged ileus, wound infection, abdominal collection and pancreatic leak, unilateral ureteric injury, sepsis and electrolyte imbalance. Reoperation was needed for ureteric necrosis, staple line bleeding and thoracic empyema
    3. A systematic review and meta-analysis of 620 patients (14 studies) with peritoneal carcinomatosis from gastric cancer reported a statistically significantly higher risk of developing postoperative complications in the HIPEC group compared with the control group (RR=2.15, 95% CI 1.29 to 3.58, p< 0.01) and this was consistent among RCTs (RR=2.88, 95% CI 1.04 to 7.97, p=0.04) and NRCTs (RR=1.86, 95% CI 1.04 to 3.33, p=0.04). HIPEC is related to a high risk of developing respiratory failure (RR=3.67, 95% CI

2.02 to 6.67, p< 0.001) and renal dysfunction (RR=4.46, 95% CI 1.42 to 13.99, p=0.01) and it is related to systemic drugs toxicity

4. In the systematic review and meta-analysis of 10,036 patients (in all 76 studies) with peritoneal carcinomatosis from colorectal cancer, the morbidity rate for CSR plus HIPEC was 33% (±13.4).

Expert guidelines

- **a. NCCN 2.2023 Ovarian Cancer**
  - **a.** Hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin (100 mg/m2) can be considered at the time of interval debulking surgery (IDS) for stage III disease treated with neoadjuvant chemotherapy (NACT)
- **b. NCCN 3.2023 Colon Cancer**
  - **a.** Patients with metastatic disease deemed possible surgical candidates should be evaluated at a high-volume center for candidacy for hyperthermic intraperitoneal chemotherapy (HIPEC). These candidates are suggested to receive chemotherapy up to 6 months, preferably in the neoadjuvant setting. Additional chemotherapy may be considered for patients who are not resectable at initial diagnosis with the possibility of converting to resectable disease
  - **b.** Cytoreductive surgery (CRS) and HIPEC are associated with morbidity and mortality, and it is imperative that a capable multidisciplinary medical team perform extensive preoperative tests to deem a patient fit for this combination therapy
- **c. NCCN 2.2023 Gastric Cancer**
  - **a.** Hyperthermic intraperitoneal chemotherapy (HIPEC) or laparoscopic HIPEC may be a therapeutic alternative for carefully selected stage IV patients in the setting of ongoing clinical trials and is under further clinical investigation
- **d. NCCN 2.2023 Peritoneal mesothelioma**
  - **a.** Cytoreductive surgery (CRS) + hyperthermic intraperitoneal chemotherapy (HIPEC) is recommended for unicavitary epithelioid peritoneal mesothelioma or well-differentiated papillary mesothelial tumor
- **e. NCCN 1.2023 Small Bowel Adenocarcinoma**
  - **a.** Based on this lack of evidence, HIPEC cannot be recommended for this population
- **f. NCCN 5.2023 Rectal Cancer**
  - **a.** HIPEC is not mentioned
- **g. NCCN 1.2024 Uterine Cancer**
  - **a.** HIPEC is not mentioned

Other payer policies

a. NICE 2021

1) Evidence on the safety of cytoreduction surgery with hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis shows frequent and serious but well-recognized complications.

Evidence on its efficacy is limited in quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research

b. UHC 2023
    1) When performed in conjunction with Cytoreductive Surgery (CRS), intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) is proven and medically necessary for treating the following conditions:
        a. Ovarian cancer following neoadjuvant chemotherapy
        b. Peritoneal mesothelioma
        c. Pseudomyxoma Peritonei (PMP) resulting from a mucus-producing tumor
        d. Peritoneal Carcinomatosis resulting from the following cancers, provided there are no extra-abdominal metastases:
            a. Adenocarcinoma of the appendix or goblet cell carcinoma
            b. Colon
            c. Rectum
    2) Due to insufficient evidence of efficacy, intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) is unproven and not medically necessary for all other indications, including but not limited to, peritoneal Carcinomatosis resulting from the following cancers:
        a. Gastric
        b. Ovarian, except as noted above
c. Aetna 2023: Aetna considers the following procedures medically necessary:
    1) Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of pseudomyxoma peritonei (including disseminated peritoneal adenomucinosis (DPAM), characterized by histologically benign peritoneal tumors that are frequently associated with an appendiceal mucinous adenoma, as well as peritoneal mucinous carcinomatosis, which are defined as disseminated mucin-producing adenocarcinomas);
    2) Cytoreductive surgery combined with HIPEC for the treatment of peritoneal mesothelioma;
    3) Cytoreductive surgery combined with HIPEC for the treatment of goblet cell carcinoid tumor;
    4) HIPEC for use with cisplatin at the time of interval debulking surgery for FIGO stage III ovarian cancer;
    5) Regional hyperthermic melphalan perfusion in members with stage II, IIIA, and stage III in-transit extremity melanoma;
    6) Sequential radiation and local/regional external hyperthermia only for the treatment of primary or metastatic cutaneous or subcutaneous superficial malignancies (e.g., superficial recurrent melanoma, chest wall recurrence of breast cancers, and cervical lymph node metastases from head and neck cancer).
d. PacificSource 2023

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1) PacificSource considers Hyperthermic Intraperitoneal Chemotherapy (HIPEC) medically necessary when used at time of or after cytoreductive (debulking) surgery for any of the following:
    a. Malignant peritoneal mesothelioma with metastasis limited to the abdominal cavity
    b. Peritoneal carcinomatosis from gastric cancer (e.g., Appendix, Colon, Rectal, Pancreatic and Gastric Cancers) without extra-abdominal metastases
    c. Pseudomyxoma Peritonei (PMP)
    d. Stage II or Stage III epithelial ovarian cancer

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HERC staff summary

One highly trusted evidence source (NICE) found that the risks of HIPEC outweighed the benefits for all cancers. The NICE evidence review found the most evidence supported the use of HIPEC for ovarian cancer, with consistent improvement in overall survival, and found some evidence for use in carcinomatosis due to colon cancer. NICE found no improvement in gastric cancer outcomes with HIPEC. NCCN recommends HIPEC only as part of their peritoneal mesothelioma treatment algorithm. NCCN states that HIPEC for ovarian cancer "can be considered at the time of interval debulking surgery (IDS) for stage III disease treated with neoadjuvant chemotherapy (NACT)," can be considered in very limited circumstances for colon cancer, and in carefully selected stage IV gastric cancer patients as a part of a trial.

HERC staff recommendations:

1. Add HIPEC to lines 157 CANCER OF COLON, RECTUM, SMALL INTESTINE AND ANUS, 238 CANCER OF OVARY, and 261 CANCER OF RETROPERITONEUM, PERITONEUM, OMENTUM AND MESENTERY
    a. **96547** Intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) procedure, including separate incision(s) and closure, when performed; first 60 minutes (List separately in addition to code for primary procedure)
    b. **96548** each additional 30 minutes
2. Adopt a new guideline for HIPEC as shown below

GUIDELINE NOTE XXX HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC)

Lines 157, 238, 261

Hyperthermic intraperitoneal chemotherapy (HIPEC) is included on these lines only when done as part of chemoreductive surgery and only for

1) Malignant peritoneal mesothelioma with metastasis limited to the abdominal cavity
2) Peritoneal carcinomatosis due to stage III ovarian cancer previously treated with neoadjuvant chemotherapy when HIPEC is done with cisplatin
3) Colon cancer with metastatic disease limited to the abdominal cavity considered to be surgical candidates after evaluation at a high-volume center

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of cytoreduction surgery with hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis

Peritoneal carcinomatosis is cancer that has spread from other parts of the body to the lining of the abdominal cavity (peritoneum). This may lead to bowel obstruction, accumulation of fluid and pain. There are 2 parts to this procedure, which is done under general anaesthesia. The first part is cytoreductive surgery, which removes all the visible cancer. The second part is chemotherapy during the surgery (intraoperative). The abdominal cavity is filled with heated (hyperthermic) chemotherapy fluid to reach any cancer cells the surgery may have missed. This fluid is drained at the end of the procedure. The aim is to reduce symptoms and improve quality of life.

Contents

2023 CPT Code Review
Low Level Laser Therapy

Codes: **97037** Application of a modality to 1 or more areas; low-level laser therapy (ie, nonthermal and non-ablative) for post-operative pain reduction

Similar code: **S8948** (Application of a modality (requiring constant provider attendance) to one or more areas; low-level laser; each 15 minutes) is on line 662/GN173

Information: Low level laser therapy (LLLT) is the application of low-level (low-power) lasers or light-emitting diodes (LEDs) to the surface of the body. LLLT is used for a variety of applications, including low back pain, rheumatoid arthritis, neck pain, various tendinopathies, and other chronic pain conditions. LLLT uses narrow-band light source which has an anti-inflammatory effect on the mucous membranes.

Oral mucositis (OM) is one of the most frequent complications arising from the cytotoxic effects of therapies for malignancies. OM results in mouth ulceration, pain, infection, dysphagia, and reduced quality of life. OM can cause treatment interruptions, narcotic analgesia, and enteral or parenteral nutrition with associated additional costs.

Recent HERC reviews:
LLLT was reviewed at several meetings in 2021 and 2022. An AHRQ 2020 systematic review, a Washington HTA 2018 report, a 2010 Cochrane review, and 2 other systematic reviews were included in the evidence considered. The conclusion of that review was "Low level laser therapy as low to very low evidence of efficacy, and most studies do not show clinically significant benefit."

Evidence
Peng 2020, Systematic review and meta-analysis of low-level laser therapy in the prevention and treatment of oral mucositis

i. N=29 studies
    1. Chemotherapy or radiotherapy or hematopoietic stem cell transplant or a combination of these therapies
    2. 26 studies on prophylactic LLLT, 6 studies on therapeutic LLLT
ii. Prophylactic LLLT reduced the overall risk of severe OM (relative risk [RR] = 0.40; 95% confidence interval [CI]: 0.28-0.57; P < .01). Therapeutic LLLT substantially reduced the duration of severe OM (P < .01). LLLT also reduced the overall mean grade of OM, overall incidence of severe pain, mean score of pain, and incidence of severe OM, at the most anticipated time.
iii. Our findings indicate that prophylactic LLLT is effective in preventing OM in patients receiving chemotherapy or radiotherapy and that therapeutic LLLT is effective in reducing severe OM duration. On the basis of the results of our risk of bias assessment and heterogeneity analysis, we believe that more well-designed multicenter RCTs on this subject are needed

Other payer policies

1. Aetna 2023 considers low level laser therapy to be experimental for all indications other than the prevention of oral mucositis in persons undergoing cancer treatment
2. Regence BCBS 2023 considers low level laser therapy to be experimental
3. Cigna 2023 considers low level laser therapy to be experimental for all indications other than the prevention of oral mucositis in persons undergoing cancer treatment
4. Providence Health Plan 2023
    a. Low-level laser therapy for the prevention of oral mucositis may be considered medically necessary for members undergoing cancer treatment associated with increased risk or oral mucositis, including chemotherapy, radiotherapy, and/or hematopoietic stem cell transplantation.
    b. Low-level laser therapy (i.e., cold laser therapy) and high-power laser therapy (i.e., class IV laser) are considered not medically necessary for all other indications

HERC staff summary

A recent HERC review in 2020 found no evidence of effectiveness for low level laser therapy (LLLT). A recent systematic review and meta-analysis found evidence that LLLT is effective at preventing and treating mucositis from cancer treatments, with the majority of the evidence on prophylaxis before mucositis occurs. Most major insurers are now covering LITT for this indication, but not for other indications.

The new CPT code is specific to use of LLLT for post-operative pain. This indication is not supported by evidence. However, the existing HCPCS code for LLLT is used for prophylaxis or treatment of oral mucositis. HERC staff recommending adding the new code to line 662/GN173 and adding coverage for the existing HCPCS code with a new guideline.

HERC staff recommendations:

1. Place CPT 97037 (Application of a modality to 1 or more areas; low-level laser therapy (ie, nonthermal and non-ablative) for post-operative pain reduction) on line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
2. Add an entry to GN173 for CPT 97037
3. Remove HCPCS S8948 (Application of a modality (requiring constant provider attendance) to one or more areas; low-level laser; each 15 minutes) from line 662 and place on all lines with chemotherapy, radiation therapy or stem cell transplant
4. Delete the entry in GN173 regarding HCPCS S8948
5. Adopt a new guideline as shown below regarding LLLT

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

Line 662

The following Interventions are prioritized on Line 662 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
~~S8948~~	~~Low level laser therapy and all similar therapies~~	~~Insufficient evidence of effectiveness~~	~~August 2020~~
97037	Application of a modality to 1 or more areas; low-level laser therapy (ie, nonthermal and non-ablative) for post-operative pain reduction	Insufficient evidence of effectiveness	November 2023

GUIDELINE NOTE XXX LOW LEVEL LASER THERAPY

All lines with chemotherapy/radiation therapy/stem cell transplant

Low level laser therapy (HCPCS S8948) is included on these lines only for prevention of oral mucositis for members undergoing cancer treatment associated with increased risk of oral mucositis, including chemotherapy, radiotherapy, and/or hematopoietic stem cell transplantation.

Low-level laser therapy in the prevention and treatment of oral mucositis: a systematic review and meta-analysis

Jiakuan Peng, Yujie Shi, Jiongke Wang, Fei Wang, Hongxia Dan, Hao Xu, and Xin Zeng

Objective. The aim of this study was to determine whether prophylactic and therapeutic low-level laser therapy (LLLT), compared with placebo or no therapy, reduced the risk of severe oral mucositis (OM) in patients receiving chemotherapy or radiotherapy.
Study Design. We searched for articles published on randomized controlled trials (RCTs) in the databases MEDLINE, EMBASE, Cochrane Library, Cochrane Central Register of Controlled Trials, Web of Science, and Clinical Trials, until December 2018. RCTs were filtered on the basis of eligibility criteria, and data were analyzed by using R software 3.5.2.
Results. Overall, 30 studies were included in the meta-analysis. Prophylactic LLLT reduced the overall risk of severe OM (relative risk [RR] = 0.40; 95% confidence interval [CI]: 0.28−0.57; $P < .01$). Therapeutic LLLT substantially reduced the duration of severe OM ($P < .01$). LLLT also reduced the overall mean grade of OM, overall incidence of severe pain, mean score of pain, and incidence of severe OM, at the most anticipated time.
Conclusions. Prophylactic and therapeutic LLLT can reduce the risk of severe OM in patients receiving chemotherapy or radiotherapy. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;130:387−397)

Oral mucositis (OM) is one of the most frequent complications arising from the cytotoxic effects of therapies for malignancies, for example, radiotherapy for head and neck squamous cell cancer (HNSCC), chemotherapy for leukemia and HNSCC, and hematopoietic stem cell transplantation (HSCT) for malignant hematologic disorders.[1-3] The incidence of OM is approximately 20% to 40% in patients receiving chemotherapy, 60% to 85% in patients undergoing allogeneic HSCT with myeloablative conditioning, and almost 100% in patients with HNSCC receiving radiotherapy.[4] The clinical manifestations of OM, which include mouth ulceration, pain, infection, and dysphagia, increase the demand for analgesia and result in the deterioration of general nutritional status and lower the quality of life.[5-7] Moreover, severe OM could result in dosage reduction, which may lead to recurrence of the disease.[8] Considering these adverse reactions of chemotherapy or radiotherapy in patients with malignancies, it is highly recommended that appropriate management of OM be taken into account during the course of therapy.

Both prophylactic and therapeutic interventions after radiotherapy-induced or chemotherapy-induced OM are continuously being discussed. Furthermore, available plans have been published by the Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology suggesting low-level laser therapy (LLLT) as an optional method to prevent and control OM caused by antitumor irradiation or medication.[9] LLLT, commonly used in physiotherapy, utilizes the effect of light energy on living cells. The light energy applied in LLLT is absorbed by cytochromes and porphyrins in mitochondria. The light triggers several pathways to activate cells, promotes cell proliferation and differentiation, and results in an accelerated regeneration process.[10] In addition, the light also triggers pathways that regulate inflammatory control and cause pain reduction.[11-13] The anti-inflammatory, analgesic, and biomodulatory effects of LLLT are considered to be beneficial in inflammatory disorders (e.g., OM).[10] This laser has a wide range of parameters, including wavelength, power, energy density, irradiation duration, and continuity among others,[14] which are essential for its effectiveness and safety.

A meta-analysis[4] summarizing a positive prophylactic effect of LLLT on OM was published in 2014; however, that analysis was focused only on the prevention of OM. To systematically evaluate both the prophylactic and therapeutic effects of LLLT in patients who might develop or have developed OM during chemotherapy or radiotherapy, we planned to integrate the latest data of clinical trials to conduct a statistical analysis.

State Key Laboratory of Oral Diseases, National Clinical Research Center for Oral Diseases, Chinese Academy of Medical Sciences Research Unit of Oral Carcinogenesis and Management, West China Hospital of Stomatology, Sichuan University, Chengdu, Sichuan, China.
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Statement of Clinical Relevance

According to the results of this meta-analysis, prophylactic and therapeutic low-level laser therapy appear to be effective in preventing and treating oral mucositis in patients receiving chemotherapy and radiotherapy.

2023 CPT Code Review
Caregiver Training

Codes:
97550 Caregiver training in strategies and techniques to facilitate the patient's functional performance in the home or community (e.g., activities of daily living [ADLs], instrumental ADLs [IADLs], transfers, mobility, communication, swallowing, feeding, problem-solving, safety practices) (without the patient present), face-to-face; initial 30 minutes

97551 each additional 15 minutes

97552 Group caregiver training

Information: Caregiver training is a part of PT, OT and speech therapy practice in which the caregiver is provided education and training to help the patient in performing specific tasks. These trainings to the caregiver include the development of skills such as safe activity completion, problem solving, environmental adaptation, training in use of equipment or assistive devices, or interventions focusing on motor, process, and communication skills. During the face-to-face service time, caregivers are taught by the treating practitioner how to facilitate the patient's activities of daily living, transfers, mobility, communication and problem-solving to reduce the negative impacts of the patient's diagnosis on the patient's daily life and assist the patient in carrying out a treatment plan.

When the patient is present for the intervention, caregiver training is covered under the CPT code that most appropriately describes the education or training activity and the patient-centered goal it addresses. Previously when the patient was not present, however, caregiver training was not able to be captured in coding for reimbursement because most CPT codes commonly used by PTs and OTs are defined as 1:1 services that require direct patient interaction. While patient engagement in caregiver training is best practice in most scenarios, there are situations where the patient's presence at the caregiver training may impede caregiver skill acquisition, negatively impact the practitioner-patient relationship, or the patient's medical condition may be such that they are physically or cognitively unable to participate in the caregiver session.

CMS has defined a caregiver as a layperson who assists in the care of the patient.

HERC staff recommendation:

a. Place CPT **97550-97552** (Caregiver training) on any line with CPT codes for PT, OT or speech therapy services (for example, 97161, 97166, 92508)

2023 CPT Code Review
Pelvic Examination Practice Expense

Code: **99459** Pelvic examination (List separately in addition to code for primary procedure)

Information: Pelvic exams are done for a variety of reasons, including screening for cervical cancer, testing for STIs, evaluating pelvic pain, and evaluation of abnormal uterine bleeding. The physician portion of the exam is included in the office visit code, as well as any procedures such as collection of a pap smear. The new pelvic examination code was requested by ACOG to capture practice expenses, particularly staff time for chaperoning the exam.

From ACOG:

> At the September 2022 American Medical Association (AMA) CPT® Editorial Panel Meeting, the Panel approved a new code to capture the practice expense (PE) of providing a clinical staff chaperone during a pelvic examination. The new CPT code 9X036 is a PE-only code, and therefore has no physician work (i.e., work relative value unit (RVU)) associated with the service. As such, the code is valued at 0.68 PE RVUs which captures four minutes of clinical staff time when chaperoning a pelvic exam. The code may be reported with evaluation and management (E/M) services in the non-facility/office setting. Note that the medical documentation must support that a pelvic exam was performed. This code should not simply be added to every female medical exam without the proper documentation.

There was no discussion of this code found in the September 2022 AMA CPT meeting minutes.

Other practice expense RVUs include expenses for building space, equipment and supplies. PE values are part of a complicated formula used to calculate physician payment, which also include values for physician work, geographic pricing index, and practice liability insurance.

From the AMA, available at https://www.ama-assn.org/system/files/practice-expense-component.pdf:

> Beginning in January 1999, Medicare began a transition to resource-based practice expense (PE) relative values, which establish PE payment for each Current Procedural Terminology (CPT®) code that differs based on the site of service. Procedures that can be performed in a physician's office, as well as in a hospital have two PE relative values: facility and nonfacility PE relative values. The nonfacility setting includes physician offices, freestanding imaging centers, and independent pathology labs. Facility settings include all other settings, such as hospitals, ambulatory surgery centers, skilled nursing facilities, and partial hospitals. In 2002, PEs were fully transitioned and the practice-expense component of the resource-based relative value scale (RBRVS) is resource-based. In 2007, the Centers for Medicare & Medicaid Services (CMS) implemented a new PE methodology.
>
> Practice expenses make up 52.2% of family physician revenues and 38.8% of obstetrician/gynecologist revenues.

HERC staff summary

Practice expense payments are part of an extraordinarily complicated calculation designed by CMS that takes into account factors such as a percent of useful life of the medical equipment, number of physician owners and employees in a practice, supply pool costs, and administrative labor costs, then multiples these factors by other weighted percentages for physician specialty, geographic location, place of

service, and supply use percentage from an AMA survey of practice overhead, then divides this by a percentage of direct work, calculates in a factor for indirect work, and then result is multiplied by a budget neutrality adjustment fraction. The result of this extremely complicated equation is then put into another extremely complicated equation that includes physician RVUs and the output is a physician payment amount. Taken all of this into account, HERC staff are unsure how this code will be operationalize and whether additional reimbursement is appropriate for this service given the nature of the RVU calculation system.

<u>HERC staff recommendation:</u>

a. Discuss whether to recommend placement on the CPT **99459** (Pelvic examination) on the Diagnostic Procedures file or the Excluded File.

2023 CPT Code Review
Limited PLA Code Review

Issue: 62 new proprietary lab analysis (PLA) codes were published as part of the 2024 new code set. In depth review of each these codes is not feasible with limited HERC staff resources. HERC staff have done a limited review of certain codes of interest. This review focused on tests for obstetrical conditions (of high interest to the OHP population) and tests/treatments substantially similar to tests/treatments previously reviewed by the HERC.

Oncology biomarkers were outside the scope of this review, due to the complex nature of the individual genes involved. Oncology next generation sequencing test PLA codes are included in a separate GAP issue summary.

NOTE: most PLA codes have never been reviewed by the HERC. When a similar PLA code was identified to one in the 2024 set, HERC staff have included that code(s) in this review.

1) **0377U** lipoprotein profile
    a. Similar codes: CPT 83695-83704 (Lipoprotein testing) are on line 662
    b. HERC staff recommendation:
        i. Place **0377U** (Cardiovascular disease, quantification of advanced serum or plasma lipoprotein profile, by nuclear magnetic resonance (NMR) spectrometry with report of a lipoprotein profile (including 23 variables)) on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
        ii. Modify the entry in GN173 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 662

The following Interventions are prioritized on Line 662 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**
83700-83704, 0377U	Lipoprotein, blood	Insufficient evidence of effectiveness	October 2006

2) **0380U** Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis, 20 gene variants and CYP2D6 deletion or duplication analysis with reported genotype and phenotype
    a. Similar code CPT 81226 CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN) is on the DIAGNOSTIC PROCEDURES file
    b. The current non-prenatal genetic testing guideline lists the following criteria for the above tests:

i. CPT 81225-81227, 81230-81231 (cytochrome P450). Covered only for determining eligibility for medication therapy if required or recommended in the FDA labelling for that medication. These tests have unproven clinical utility for decisions regarding medications when not required in the FDA labeling (e.g. psychiatric, anticoagulant, opioids).

c. HERC staff recommendations:
   i. Place **0308U** (Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis, 20 gene variants and CYP2D6 deletion or duplication analysis with reported genotype and phenotype) on the DIAGNOSTIC PROCEDURES file
   ii. Modify the entry in DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE to read as below

CPT 81225-81227, 81230-81231**,** 81418, 0308U (cytochrome P450). Covered only for determining eligibility for medication therapy if required or recommended in the FDA labelling for that medication. These tests have unproven clinical utility for decisions regarding medications when not required in the FDA labeling (e.g. psychiatric, anticoagulant, opioids).

3) **0390U, 0243U** Maternal serum biomarker for prediction of risk for preeclampsia
   a. Information: preeclampsia is a serious complication of pregnancy and can cause maternal and perinatal morbidity and mortality. Standard screening for preeclampsia is monitoring blood pressure, urinalyses, and blood tests. Maternal serum biomarker testing is proposed as an adjunct to standard screening to identify women at risk of preeclampsia
   b. Codes
      i. Older code
         1. 0243U Obstetrics (preeclampsia), biochemical assay of placental-growth factor, time-resolved fluorescence immunoassay, maternal serum, predictive algorithm reported as a risk score for preeclampsia
            a. PGIF Preeclampsia Screen
      ii. 2024 code
         1. 0390U Obstetrics (preeclampsia), kinase insert domain receptor (KDR), Endoglin (ENG), and retinol-binding protein 4 (RBP4), by immunoassay, serum, algorithm reported as a risk score
            a. PEPredictDx
   c. Expert guidelines
      i. **ACOG 2020**, practice bulletin on gestational hypertension and preeclampsia
         1. Several studies have evaluated the role of biochemical markers or a combination of biochemical and biophysical markers in the prediction of preeclampsia in the first and second trimesters of pregnancy (79). Regardless of the parameters used, screening for preeclampsia in low-risk women is associated with very low positive predictive values ranging from 8% to 33%

2. However, no single test reliably predicts preeclampsia and further prospective investigation is required to demonstrate clinical utility
3. Thus, biomarkers and ultrasonography cannot accurately predict preeclampsia and should remain investigational.

d. Other payer polcies:
   i. Premara BCBS 2023
      1. The use of maternal serum biomarker tests with or without additional algorithmic analysis for prediction of preeclampsia is considered investigational.
   ii. Aetna 2023 considers PEPredictDx to be experimental
e. HERC staff summary: maternal serum biomarkers for preeclampsia risk are not recommended for use by ACOG
f. HERC staff recommendation
   i. Place **0390U, 0243U** on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
   ii. Add an entry to GN173 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 662

The following Interventions are prioritized on Line 662 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
0390U, 0243U	Maternal serum biomarker tests with or without additional algorithmic analysis for prediction of preeclampsia	Insufficient evidence of effectiveness	November 2023

4) **0392U, 0411U, 0419U** Drug metabolism testing for psychiatric conditions
   a. Codes
      i. 0392U Drug metabolism (depression, anxiety, attention deficit hyperactivity disorder [ADHD]), gene-drug interactions, variant analysis of 16 genes, including deletion/duplication analysis of CYP2D6, reported as impact of gene-drug interaction for each drug
      ii. 0411U Psychiatry (eg, depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6
      iii. 0419U Neuropsychiatry (eg, depression, anxiety), genomic sequence analysis panel, variant analysis of 13 genes, saliva or buccal swab, report of each gene phenotype
   b. Current Prioritized List status/older codes

i. 0173U Psychiatry (ie, depression, anxiety), genomic analysis panel, includes variant analysis of 14 genes
ii. 0175U Psychiatry (eg, depression, anxiety), genomic analysis panel, variant analysis of 15 genes
iii. 0345U Psychiatry (eg, depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6
iv. General gene testing for cytochrome P450 testing is covered, with an entry in the non-prenatal genetic testing guideline stating that such testing cannot be for psychiatric medications when not required in the FDA labeling

DIAGNOSTIC GUIDELINE D21, PHARMACOGENETICS TESTING FOR PSYCHIATRIC MEDICATION MANAGEMENT
Pharmacogenetics testing for management of psychiatric medications is not a covered service.

c. HERC staff recommendation
   i. Place **0173U, 0175U, 0345U, 0392U, 0411U, and 0419U** on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
   ii. Add an entry to GN173 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 662

The following Interventions are prioritized on Line 662 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
0173U, 0175U, 0345U, 0392U, 0411U, 0419U	Pharmacogenetics testing for management of psychiatric medications	Insufficient evidence of effectiveness	November 2023

5) **0396U** Pre-implantation genetic testing
   a. Infertility and IVF is an excluded service
   b. Older similar PLA codes
      i. 0253U Reproductive medicine (endometrial receptivity analysis), RNA gene expression profile, 238 genes by next-generation sequencing, endometrial tissue, predictive algorithm reported as endometrial window of implantation (eg, pre-receptive, receptive, post-receptive)
      ii. 0254U Reproductive medicine (preimplantation genetic assessment), analysis of 24 chromosomes using embryonic DNA genomic sequence analysis for

aneuploidy, and a mitochondrial DNA score in euploid embryos, results reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplication, mosaicism, and segmental aneuploidy, per embryo tested

c. HERC staff recommendations:
    i. Place **0396U** (Obstetrics (pre-implantation genetic testing), evaluation of 300000 DNA single-nucleotide polymorphisms (SNPs) by microarray, embryonic tissue, algorithm reported as a probability for single-gene germline conditions) on the Excluded file
    ii. Place **0253U, 0254U** on the Excluded file

6) **0408U** Omnia COVID test
    a. All other COVID tests are considered diagnostic
    b. 0408U codes for the Qorvo Biotechnologies Omnia COVID antigen test, which tests for COVID antigen directly from a nasal swab without the use of transport media
    c. The Omnia test received an EUA from the FDA in July 2022
    d. HERC staff recommendation:
        i. Place 0408U (Infectious agent antigen detection by bulk acoustic wave biosensor immunoassay, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19])) on the Diagnostic Procedures file

ACOG
The American College of Obstetricians and Gynecologists

ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 222

(Replaces Practice Bulletin No. 202, December 2018)

Committee on Practice Bulletins—Obstetrics. This Practice Bulletin was developed by the American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics in collaboration with Jimmy Espinoza, MD, MSc; Alex Vidaeff, MD, MPH; Christian M. Pettker, MD; and Hyagriv Simhan, MD.

INTERIM UPDATE: The content of this Practice Bulletin has been updated as highlighted (or removed as necessary) to include limited, focused editorial corrections to platelet counts, diagnostic criteria for preeclampsia (Box 2), and preeclampsia with severe features (Box 3).

Gestational Hypertension and Preeclampsia

Hypertensive disorders of pregnancy constitute one of the leading causes of maternal and perinatal mortality worldwide. It has been estimated that preeclampsia complicates 2–8% of pregnancies globally (1). In Latin America and the Caribbean, hypertensive disorders are responsible for almost 26% of maternal deaths, whereas in Africa and Asia they contribute to 9% of deaths. Although maternal mortality is much lower in high-income countries than in developing countries, 16% of maternal deaths can be attributed to hypertensive disorders (1, 2). In the United States, the rate of preeclampsia increased by 25% between 1987 and 2004 (3). Moreover, in comparison with women giving birth in 1980, those giving birth in 2003 were at 6.7-fold increased risk of severe preeclampsia (4). This complication is costly: one study reported that in 2012 in the United States, the estimated cost of preeclampsia within the first 12 months of delivery was $2.18 billion ($1.03 billion for women and $1.15 billion for infants), which was disproportionately borne by premature births (5). This Practice Bulletin will provide guidelines for the diagnosis and management of gestational hypertension and preeclampsia.

Background

Risk Factors

A variety of risk factors have been associated with increased probability of preeclampsia (Box 1) (6–12). Nonetheless, it is important to remember that most cases of preeclampsia occur in healthy nulliparous women with no obvious risk factors. Although the precise role of genetic–environmental interactions on the risk and incidence of preeclampsia is unclear, emerging data suggest the tendency to develop preeclampsia may have some genetic component (13–16).

Definitions and Diagnostic Criteria for Hypertensive Disorders of Pregnancy

Preeclampsia (With and Without Severe Features)

Preeclampsia is a disorder of pregnancy associated with new-onset hypertension, which occurs most often after 20 weeks of gestation and frequently near term. Although often accompanied by new-onset proteinuria, hypertension and other signs or symptoms of preeclampsia may present in some women in the absence of proteinuria (17). Reliance on maternal symptoms may be occasionally problematic in clinical practice. Right upper quadrant or epigastric

Section 10.0

Previously Discussed Items

Breast Reduction for Macromastia

Plain Language Summary:

Coverage question: Should OHP cover surgery to reduce the size of breasts when they cause back and/or neck pain?

Should OHP cover this treatment? Yes, when there are no other reasons for the neck and back pain, and in situations where the surgery seems likely to help with the neck and back pain this surgery should be covered.

Coverage Question: Should coverage be added for breast reduction surgery for macromastia?

Question source: OHP Ombuds office

Background: The ombuds office has had multiple cases in which women were seeking breast reduction for treatment of back or neck pain or other painful conditions related to large breasts.

Currently, macromastia is on an unfunded line on the Prioritized List, Line 653 MACROMASTIA/BREAST REDUCTION. There is a guideline on the Prioritized List that prohibits coverage for breast reduction (Guideline Note 166). Breast reduction is covered on the breast cancer line for symmetry of the reconstructed breast and natural breast; this coverage is mandated by federal rule. Breast reduction is also covered for gender affirmation.

Macromastia is defined as large breasts, generally considered larger than a D cup although various other definitions may be used. Macromastia can cause various physical symptoms, including headache, neck pain, back pain, and shoulder pain. Breast reduction is used to reduce the size of the breasts and is one of the most commonly performed cosmetic surgeries in the US.

This topic was discussed at the March 2023 VBBS and HERC meetings. The VBBS requested that staff obtain expert input on the evidence regarding effectiveness of this procedure and bring back for further consideration.

The topic was again discussed at the August 2023 VBBS and HERC meetings. The VBBS agreed that coverage should be added as a two step process: 1) change the breast reduction guideline to allow coverage as a co-morbid condition to neck and back pain and to include adolescents in this guideline based on wording from other state Medicaid program coverage; then 2) reprioritize the macromastia line as part of the 2026 biennial review. The HERC requested consideration of wording regarding the expected amount of tissue to be removed to be included in the guideline. HERC members were also interested in having OMT and acupuncture included as conservative therapy options.

Macromastia was again discussed at the September 2023 VBBS and HERC meetings. At the September meeting, both VBBS and HERC agreed that macromastia should be covered for 1) shoulder pain, 2) back and neck pain, and 3) intertrigo when guideline criteria are met. To make this coverage clear, VBBS

members directed staff to draft a proposal to add all of the diagnosis and procedure codes from the current macromastia line to the covered back pain, shoulder issue, and inflammatory skin disease lines, effective 1/1/24. During the 2026 Biennial Review, the current macromastia line will be reprioritized to have symptomatic macromastia in the funded region and asymptomatic macromastia added to the musculoskeletal conditions with no treatment necessary line, with appropriate modifications to the macromastia guideline, and undo the duplicate coding on the back, shoulder, and skin disease lines.

Current Prioritized List/Coverage status:

CPT 19318 (Reduction mammaplasty) is on lines 191 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER, 312 GENDER DYSPHORIA/TRANSEXUALISM, and 561 MACROMASTIA.

ICD-10 N62 (Hypertrophy of breast) is on lines 561 MACROMASTIA and 642 GYNECOMASTIA

Line:	**561**
Condition:	MACROMASTIA (See Guideline Notes 196 and 166)
Treatment:	BREAST REDUCTION
ICD-10:	N62
CPT:	19318,98966-98972,99051,99060,99070,99078,99184,99202-99239,99281-99285,99291-99404,99411-99449,99451,99452,99468-99472,99475-99480,99487-99491,99495-99498,99605-99607
HCPCS:	G0068,G0071,G0088-G0090,G0248-G0250,G0406-G0408,G0425-G0427,G0463,G0466,G0467,G0490,G0508-G0511,G2012,G2211,G2212,G2214,G2251,G2252

GUIDELINE NOTE 166, BREAST REDUCTION SURGERY FOR MACROMASTIA

Lines 402,561

Breast reduction surgery for macromastia is not covered as a treatment for neck or back pain resulting from the macromastia due to lack of high quality evidence of effectiveness.

Breast Reduction for Macromastia

HERC staff summary:

VBBS and HERC have directed staff to design a proposal to add the macromastia diagnoses and procedures to the covered back, shoulder, and inflammatory skin disease lines with a new guideline modified based on the discussion at the September, 2023 meetings.

On review, line 561 contains one unique ICD-10-CM code (N62 Hypertrophy of breast) and one CPT code specific to breast reduction (19318 Breast reduction). The other CPT and HCPCS codes on line 561 are generic office and hospital codes that already appear on the back, shoulder and inflammatory skin disease lines.

Intertrigo is coded with ICD-10-CM L30.4 (Erythema intertrigo) which is on line 504 ERYTHEMATOUS CONDITIONS.

HERC staff recommendations (effective 1/1/2024):

1) Add ICD-10-CM N62 (Hypertrophy of breast) and CPT 19318 (Breast reduction) to the following lines:
    a. 402 CONDITIONS OF THE BACK AND SPINE
    b. 417 DISORDERS OF SHOULDER, INCLUDING SPRAINS/STRAINS GRADE 4 THROUGH 6
    c. 426 SEVERE INFLAMMATORY SKIN DISEASE
2) Adopt a new guideline for breast reduction for macromastia as shown below
3) Add ICD-10-CM L30.4 (Erythema intertrigo) to line 426 SEVERE INFLAMMATORY SKIN DISEASE

GUIDELINE NOTE 166, BREAST REDUCTION SURGERY FOR SYMPTOMATIC MACROMASTIA

Lines 402,417,426,561

~~Breast reduction surgery for macromastia is not covered as a treatment for neck or back pain resulting from the macromastia due to lack of high quality evidence of effectiveness.~~

Breast reduction surgery is included on these lines 402, 417 or 426 only when ALL of the following conditions are met:

1) The patient is aged 15 or older; AND
2) The patient has a diagnosis of macromastia (size D or higher); AND
3) At least one of the following criteria (a or b) have been met:
    a. Back, neck or shoulder pain
        i. Must be documented to have adverse effects on activities of daily living
        ii. Must be unresponsive to conservative treatments for three months within a year prior. Conservative treatment must include at least three months of
            1. a documented trial of analgesics, AND
            2. physical therapy or chiropractic/osteopathic manipulation treatment or acupuncture, AND
            3. use of support wear for the breast; OR
    b. Persistent severe intertrigo in the inframammary fold unresponsive to documented prescribed medication for at least three months within a year prior; AND
4) The treating surgeon must document that breast reduction has a high likelihood of improving the symptoms that limit activities of daily living caused by the macromastia; AND

Breast Reduction for Macromastia

5) The expected bilateral reduction volume must be greater than 300 grams (1 cup size) per breast; AND
6) Women aged 40 and older are required to have a negative screening mammogram within two years of the planned reduction mammoplasty; AND
7) Member should be a non-smoker or should not have smoked within the 6 weeks prior to surgery as documented by the surgeon.

Additional criteria for patients aged 15-17 years:

1) The patient must have completed puberty (Tanner stage V)
2) The patient must have a one year history of growth stabilization evidenced by a minimum of four visits with documented heights or puberty completion as shown on wrist radiograph read by a radiologist

Otherwise, breast reduction surgery is included on line 561.

Gender Affirming Treatment Standard of Care

Plain Language Summary:

Coverage question: Should OHP pick a "standard of care" for gender affirming treatments?

Should OHP cover this treatment? Yes, OHP should use the World Professional Association for Transgender Health (WPATH) Standards of Care 8.0.

Coverage Question: Should guideline note 127 be modified to reference a specific standard of care for gender affirming treatments?

Question source: Public comment from the August 17, 2023 HERC and VBBS meetings

Previous HERC reviews:

In 2015, HERC approved coverage for puberty-suppressing medications for gender-questioning youth. In 2016, based on a HERC decision, the Oregon Health Plan (OHP) began covering a set of services based on standards of care developed by the World Professional Association of Transgender Health (WPATH; Version 7.0). These standards included a variety of chest and genital surgeries as well as medications.

In late 2022, WPATH published Version 8.0 of its standards of care, which broadened the scope of services and included changes to the assessments required in order to receive certain services. In early 2023, HERC staff was working on an updated evidence review and potential recommended changes to the services covered on OHP and had planned to bring this to the August 17, 2023 meetings of the Value-based Benefits Subcommittee (VbBS) and the Health Evidence Review Commission (HERC), knowing that the discussion may require multiple meetings.

In June of 2023, before this work was completed, the legislature passed HB 2002, which required coverage of gender-affirming treatments and prohibited denials of gender-affirming treatments when prescribed in alignment with accepted standards of care. The bill takes effect January 1, 2024.

During its August 2023, meeting, HERC revised its guideline note 127 to reference HB 2002 and added codes to Line 312 of the Prioritized List based on the services listed in WPATH 8.0. At the same August meeting, several individuals (including patients and a health plan representative) offered written and verbal comment requesting that HERC reference the WPATH 8.0 standards of care as the accepted standard of care for OHP. Staff followed up with legislative research and legal consultation and concluded that reference to WPATH 8.0 is appropriate in order to implement HB 2002.

Professional guidelines:

World Professional Association for Transgender Health. (2022). Standards of Care version 8. Retrieved from https://www.tandfonline.com/doi/pdf/10.1080/26895269.2022.2100644

Gender Affirming Treatment Standard of Care

Pending Prioritized List/Coverage status (planned for implementation 1/1/2024):

Line:	312
Condition:	GENDER DYSPHORIA/TRANSEXUALISM (See Guideline Notes 127 and 196)
Treatment:	MEDICAL AND SURGICAL TREATMENT/PSYCHOTHERAPY

GUIDELINE NOTE 127 GENDER AFFIRMING TREATMENT [as it will appear on the 1/1/2024 Prioritized List unless revised]
Line 312
Gender-affirming treatments are included on this line according to the provisions of House Bill 2002 (2023), whether or not the code for the service appears on the line. These services are included for gender affirming treatment or for any condition represented on this line. To simplify administration, the line includes a variety of procedures that may be considered medically necessary and prescribed in accordance with accepted standards of care.

Gender affirming treatments not on this line must also be covered in accordance with the provisions of the bill, which specify criteria for medical necessity, prohibit denying or limiting services considered by plans to be 'cosmetic' and require that any denial or limit be reviewed and upheld by a provider with experience prescribing or delivering gender affirming treatment.

HERC staff recommendation:

1) Revise Guideline note 127 as shown below.

GUIDELINE NOTE 127 GENDER AFFIRMING TREATMENT
Line 312
Gender-affirming treatments are included on this line according to the provisions of House Bill 2002 (2023), when provided according to Standards of Care for the Health of Transgender and Gender Diverse People, Version 8, published by the World Professional Association of Transgender Health (WPATH), whether or not the code for the service appears on the line. These services are included for gender affirming treatment or for any condition represented on this line. To simplify administration, the line includes a variety of procedures that may be considered medically necessary and prescribed in accordance with the WPATH 8.0 standards of care.

Gender affirming treatments billed using CPT or HCPCS codes not on this line must also be covered in accordance with the provisions of the bill.

In addition, the bill prohibits denial or limitation of services determined to be medically necessary by the provider who prescribed the treatment, ~~criteria for medical necessity,~~ prohibits denying or limiting services considered by plans to be 'cosmetic' and requires that any denial or limit be reviewed and upheld by a provider with experience prescribing or delivering gender affirming treatment.

Tobacco Cessation Requirements in Prioritized List Guidelines

Plain Language Summary:

Coverage question: Should OHP members have to stop smoking or using nicotine before they can have certain types of surgery?

Should OHP cover this treatment? Yes, with some changes for spinal fusion and lung surgery for COPD. No, for surgery for erectile dysfunction.

Coverage Question: Should any of the tobacco cessation requirements in Prioritized List guidelines be modified?

Question source: VBBS/HERC

Background: During 2023, the guideline on smoking cessation and elective surgery was extensively edited and became a Statement of Intent. Tobacco cessation should be encouraged before any elective surgery, but it is no longer required. This change was made due to unintended harms of the previous policy, preventing OHP patients from getting specialist consultations or needed treatments.

VBBS and HERC members requested that HERC staff examine the remaining guidelines that have some type of requirement for tobacco cessation. Specifically, HERC staff were directed to determine if tobacco smoking should be the focus of the cessation or whether nicotine cessation is required (which would include nicotine patches). Members noted that the current wording in various guidelines was quite different, and directed staff to see if any standardization of language should be done. If not, staff were directed to review evidence that a particular procedure, such as spinal fusion, had significantly poorer outcomes with smoking and/or using nicotine.

Previous HSC/HERC reviews:

Tobacco cessation for spinal fusion has been discussed multiple times beginning in 2012, when a guideline was added to the prioritized List restricting spinal fusion to non-smokers due to the evidence of non-fusion in smokers. Initially, the guideline simply read that spinal fusion was limited to patients who were non-smoking 6 months prior to the procedure (no mention of nicotine replacement use or objective testing). Objective testing requirements were added later.

The non-smoking requirement was added to the lung volume reduction surgery guideline in 2015 after an evidence review.

During a larger discussion of smoking and elective surgery in November 2015, VBBS members expressed a desire to have a guideline not allowing smoking prior to erectile dysfunction surgery due to member feeling that this surgery was highly affected by smoking. No evidence was reviewed at that time. In

Tobacco Cessation Requirements in Prioritized List Guidelines

October 2016, a new guideline regarding smoking and erectile surgery was added. The rationale was "based on the November VBBS discussion" with no evidence review.

Current Prioritized List/Coverage status:

STATEMENT OF INTENT 8: SMOKING CESSATION AND ELECTIVE SURGICAL PROCEDURES

Tobacco smoking has been shown to increase the risk of surgical complications. It is the intent of the Commission that current tobacco smokers should be given access to appropriate smoking cessation therapy prior to elective surgical procedures. Pharmacotherapy (including varenicline, bupropion and all five FDA-approved forms of nicotine-replacement therapy) and behavioral counseling are included on Line 5 TOBACCO DEPENDENCE.

GUIDELINE NOTE 8, BARIATRIC SURGERY

Line 320

Bariatric/metabolic surgery (limited to Roux-en-Y gastric bypass, sleeve gastrectomy, biliopancreatic duodenal switch, one anastomosis gastric bypass, single anastomosis duodenal-ileal bypass with gastrectomy) is included on Line 320 with specific criteria for adults and adolescents:

A) For adults aged $\geq$ 18 when ALL of the following criteria are met:
   1) The patient has obesity with a:
      a) BMI $\geq$ 35 kg/m^2; OR
      b) BMI $\geq$ 30-34.9 kg/m^2 with Type 2 Diabetes Mellitus which has not met clinical glycemia targets as defined by HbA1c of 8.0% or greater, despite trials of two diabetes medications
   2) Participate in an evaluation by a multidisciplinary team in an MBSAQIP-accredited specialty center[1]:
      a) Psychosocial (conducted by a licensed mental health professional)
      b) Medical (conducted by a primary care clinician/member of the multidisciplinary team to optimize control of comorbid conditions)
      c) Surgical (conducted by a bariatric surgeon)
      d) Nutritional (conducted by a licensed dietician)
   3) Free from active substance use disorder
   4) Free from active use of combustible cigarettes
   5) Not currently pregnant and documented counseling regarding the need for use of effective contraception for at least 18 months postoperatively, where indicated
   6) Agree to adhere to post-surgical evaluation and post-operative care recommendations, some of which may require lifelong adherence

B) For adolescents aged 13 to 17 years old when ALL of the following criteria are met:
   1) The patient has obesity with a:
      a) BMI $\geq$ 35 kg/m^2 or 120% of the 95th percentile for age and sex AND a clinically significant comorbid condition; OR
      b) BMI $\geq$ 40 kg/m^2 or 140% of the 95th percentile for age and sex
   2) Participate in an evaluation by a multidisciplinary team in an MBSAQIP-accredited specialty center with Adolescent accreditation:
      a) Psychosocial (conducted by a licensed mental health professional)

b) Medical (conducted by a primary care clinician/member of the multidisciplinary team to optimize control of comorbid conditions)
c) Surgical (conducted by a bariatric surgeon)
d) Nutritional (conducted by a licensed dietician)

3) Agree to adhere to post-surgical evaluation and post-operative care recommendations, some of which may require lifelong adherence
4) Free from active substance use disorder
5) Free from active use of combustible cigarettes
6) Not currently pregnant and documented counseling regarding the need for use of effective contraception for at least 18 months postoperatively, where indicated

Repeat bariatric surgery is included when it is a conversion from a less intensive (such as gastric band or sleeve gastrectomy) to a more intensive surgery (e.g. Roux-en-Y). Repair of surgical complications (excluding failure to lose sufficient weight) are also included on this and other lines. Reversal of surgical procedures and devices is included on this line when benefits of reversal outweigh harms.

CPT 43999 (Unlisted procedure, stomach) is only included on this line when used for single anastomosis duodenal-ileal bypass with sleeve (SADI-S). It is not included on this line for gastric balloons.

[1] All surgical services must be provided by a program with current accreditation (as a comprehensive center or low acuity center) by the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP).

GUIDELINE NOTE 42, SOLID ORGAN TRANSPLANTS [excerpt]

Lines 83,99,162,239-241,250,263,264,307,310,563

Solid organ transplants are included on these lines only when BOTH the general criteria AND the organ specific criteria below are met:

GENERAL TRANSPLANT CRITERIA

A) The patient must have irreversible end-stage organ disease or failure and must have medical therapy optimized; AND

B) The patient is a suitable surgical candidate for transplant surgery, included by ALL of the following:

1) No significant uncontrolled co-morbidities such as (not an all-inclusive list):
   a. End-stage cardiac, renal, hepatic or other organ dysfunction unrelated to the primary indication for transplant
   b. Uncontrolled HIV infection
   c. Multiple organ compromise secondary to infection, malignancy, or condition with no known cure
   d. Ongoing or recurrent active infections that are not effectively treated
   e. Psychiatric instability severe enough to jeopardize adherence to medical regimen
   f. Active alcohol or illicit drug dependency; AND
2) No tobacco smoking as determined by the transplant program unless the transplant is done on an emergent basis (other than for corneal transplants); AND

3) Demonstrated compliance with medical treatments and ability to understand and comply with the post-transplant
immunosuppressive regimen

GUIDELINE NOTE 100, SMOKING AND SPINAL FUSION

Lines 47,150,200,254,346,361,401,478,530,559

Non-emergent spinal arthrodesis (CPT 22532-22634) is limited to patients who are non-smoking and abstinent from all nicotine products for 6 months prior to the planned procedure, as shown by negative cotinine levels at least 6 months apart, with the second test within 1 month of the surgery date. Patients should be given access to appropriate smoking cessation therapy. Non-emergent spinal arthrodesis is defined as surgery for a patient with a lack of myelopathy or rapidly declining neurological exam.

GUIDELINE NOTE 112, LUNG VOLUME REDUCTION SURGERY

Line 283

Lung volume reduction surgery (LVRS, CPT 32491, 32672) is included on Line 283 only for treatment of patients with radiological evidence of severe bilateral upper lobe predominant emphysema (ICD-10-CM J43.9) and all of the following:

A) BMI ≤31.1 kg/m2 (men) or ≤32.3 kg/m 2 (women)
B) Stable with ≤20 mg prednisone (or equivalent) dose a day
C) Pulmonary function testing showing
    1) Forced expiratory volume in one second (FEV 1) ≤ 45% predicted and, if age 70 or older, FEV 1≥ 15% predicted value
    2) Total lung capacity (TLC) ≥ 100% predicted post-bronchodilator
    3) Residual volume (RV) ≥ 150% predicted post-bronchodilator
D) PCO_2, ≤ 60 mm Hg (PCO 2, ≤ 55 mm Hg if 1-mile above sea level)
E) PO_2, ≥ 45 mm Hg on room air (PO 2, ≥ 30 mm Hg if 1-mile above sea level)
F) Post-rehabilitation 6-min walk of ≥ 140 m
G) Non-smoking and abstinence from all nicotine products for 6 months prior to surgery, as shown by negative cotinine levels at least 6 months apart, with the second test within 1 month of the surgery date.

The procedure must be performed at an approved facility (1) certified by the Joint Commission on Accreditation of Healthcare Organizations (Joint Commission) under the LVRS Disease Specific Care Certification Program or (2) approved as Medicare lung or heart-lung transplantation hospitals. The patient must have approval for surgery by pulmonary physician, thoracic surgeon, and anesthesiologist post-rehabilitation. The patient must have approval for surgery by cardiologist if any of the following are present: unstable angina; left-ventricular ejection fraction (LVEF) cannot be estimated from the echocardiogram; LVEF <45%; dobutamine-radionuclide cardiac scan indicates coronary artery disease or ventricular dysfunction; arrhythmia (>5 premature ventricular contractions per minute; cardiac rhythm other than sinus; premature ventricular contractions on EKG at rest).

Tobacco Cessation Requirements in Prioritized List Guidelines

GUIDELINE NOTE 159, SMOKING AND SURGICAL TREATMENT OF ERECTILE DYSFUNCTION

Line 523

Surgical treatment of erectile dysfunction is only included on this line when patients are non-smoking and abstinent from all nicotine products for 6 months prior to surgery, as shown by negative cotinine levels at least 6 months apart, with the second test within 1 month of the surgery date

GUIDELINE NOTE 166, BREAST REDUCTION SURGERY FOR SYMPTOMATIC MACROMASTIA

Lines 402,417,426,561

Breast reduction surgery is included on these lines 402, 417 or 426 only when ALL of the following conditions are met:

1) The patient is aged 15 or older; AND
2) The patient has a diagnosis of macromastia (size D or higher); AND
3) At least one of the following criteria (a or b) have been met:
    a. Back, neck or shoulder pain
        i. Must be documented to have adverse effects on activities of daily living
        ii. Must be unresponsive to conservative treatments for three months within a year prior. Conservative treatment must include at least three months of
            1. a documented trial of analgesics, AND
            2. physical therapy or chiropractic/osteopathic manipulation treatment or acupuncture, AND
            3. use of support wear for the breast; OR
    b. Persistent severe intertrigo in the inframammary fold unresponsive to documented prescribed medication for at least three months within a year prior; AND
4) The treating surgeon must document that breast reduction has a high likelihood of improving the symptoms that limit activities of daily living caused by the macromastia; AND
5) The expected bilateral reduction volume must be greater than 300 grams (1 cup size) per breast; AND
6) Women aged 40 and older are required to have a negative screening mammogram within two years of the planned reduction mammoplasty; AND
7) Member should be a non-smoker or should not have smoked within the 6 weeks prior to surgery as documented by the surgeon.

Additional criteria for patients aged 15-17 years:

1) The patient must have completed puberty (Tanner stage V)
2) The patient must have a one year history of growth stabilization evidenced by a minimum of four visits with documented heights or puberty completion as shown on wrist radiograph read by a radiologist

Otherwise, breast reduction surgery is included on line 561.

GUIDELINE NOTE XXX ENDOBRONCHIAL VALVES

Line 283

Endobronchial valves (CPT 31647-31649 and 31651) are only included on this line when ALL of the following criteria are met:

Tobacco Cessation Requirements in Prioritized List Guidelines

1) The patient has severe heterogeneous or homogeneous emphysema
   a) Severe emphysema is demonstrated by pulmonary function testing showing
      i) Forced expiratory volume in one second (FEV 1) ≤ 45% predicted and, if age 70 or older, FEV 1≥ 15% predicted value
      ii) Total lung capacity (TLC) ≥ 100% predicted post-bronchodilator
      iii) Residual volume (RV) ≥ 150% predicted post-bronchodilator
2) The patient has significant hyperinflation in regions of the lung that have little to no collateral ventilation
3) The patient is receiving optimized medical care
4) The patient is stable with ≤20 mg prednisone (or equivalent) dose a day
5) The patient has participated in pulmonary rehabilitation and has a post-rehabilitation 6-min walk of ≥ 140 m
6) The patient is a non-smoker as determined by the performing provider

Evidence:

Spinal fusion--smoking

1) **Nunna 2022** systematic review and meta-analysis of smoking on spinal fusion rate
   a) N=20 studies (3009 patients)
      i) 1117 smokers (37%)
   b) Pooled analysis found that smoking was associated with increased risk of nonunion compared to not smoking ≥1 year following spine surgery (RR 1.91, 95% CI 1.56 to 2.35). (Strength of Evidence, Moderate)
      i) The absolute RD (excess risk) for nonunion associated with smoking was .13 and the number needed to treat (NNT) for an additional nonunion of 8 (95% CI 6 to 13).
   c) This association was seen both in the cervical spine (10 studies) pooled RR 2.03, 95% CI 1.46 to 2.81, I 2 =36%) and the lumbar spine (9 studies) pooled RR 1.78, 95% CI 1.37 to 2.31, I2 = 16). The RD for cervical and thoracolumbar fusion was .14 and .11, respectively. This relationship held true whether the follow-up was 12- 23 months or ≥24 months (Table 4), or when 9 poor-quality trials were excluded (10 studies, RR 1.74, 95% CI 1.37 to 2.21, I2 = 0%)
   d) Smoking was significantly associated with increased nonunion in those receiving either allograft (RR 1.39, 95% CI 1.12 to 1.73) or autograft (RR 2.04, 95% CI 1.54 to 2.72). Both multilevel and single level fusions carried increased risk of nonunion in smokers (RR 2.30, 95% CI 1.64 to 3.23; RR 1.79, 95% CI 1.12 to 2.86, respectively).
   e) Conclusion: Tobacco smoking status carries a global risk of nonunion for spinal fusion procedures regardless of follow-up time, location, number of segments fused, or grafting material
2) **Li 2021** systematic review and meta-analysis of smoking on spinal fusion rate
   a) N=26 studies (case control and cohort studies), 4409 patients
      i) Cervical, thoracolumbar and lumbar/sacral
   b) the pooled results demonstrated that the fusion rate of smokers after spinal fusion was significantly lower than that of nonsmokers. The odds ratio (OR) was 0.55 (95% confidence interval [CI] 0.45-0.67, P < 0.0001).
      i) There was no heterogeneity detected (I2 ¼ 2 %, P ¼ 0.43)
   c) The present meta-analysis of 26 observational studies revealed that smokers have a lower fusion rate than nonsmokers in spinal fusion surgery (OR 0.55, 95% CI 0.45-0.67, P < 0.00001). This estimate was robust across sensitivity analyses.

Tobacco Cessation Requirements in Prioritized List Guidelines

Spinal fusion—nicotine replacement therapy (NRT)

1) **Khalid 2022**, impact of smoking cessation therapy on **lumbar** fusion outcomes
    a. Matched cohort study of 31,935 patients undergoing single-level lumbar fusion
        i. 10,645 (33%) in each of the following groups: (1) active smokers; (2) patients on smoking cessation therapy; and (3) those without any smoking history
    b. The rate of any complication within 30 days of surgery was significantly higher in the smoking cohort (19%) compared with both the smoking cessation cohort (17%) and the nonsmoking cohort (9.5%). The rate of pseudarthrosis [failure of fusion] within 2.5 years of surgery was no different between the smoking (5.9%) and smoking cessation (6.1%) cohorts but was significantly lower in the nonsmoking (3.9%) cohort. Similarly, the rate of revision surgery within 2.5 years of surgery was not significantly different between the smoking (2.3%) and cessation (2.0%) cohorts but was significantly lower in the nonsmoking (1.6%) group
    c. Conclusion: both smoking and NRT had a negative effect on lumbar fusion rates and on all cause post-operative complications
2) **Khalid 2022**, impact of smoking cessation therapy on **cervical** fusion outcomes
    a. Matched cohort study of 5769 patients undergoing single-level ACDF
        i. 1923 (33.33%) in each of the following groups: (1) nonsmokers; (2) active smokers; and (3) patients undergoing smoking cessation therapy.
    b. Nonsmokers had significantly lower rates of all complications compared to active smokers and those on cessation therapy (3.74% vs 13.05% vs 15.08%).
    c. There was no significant difference in the rate of 30-day readmission (3.07% vs. 3.02% vs. 3.02%), 90-day readmission (4.68% vs. 5.25% vs 5.62%), or pseudarthrosis [failure of fusion] (3.02% vs 3.28% vs 3.17%) between the nonsmoking, active smoking, and smoking cessation groups, respectively
    d. Conclusion: NRT did not affect cervical fusion rates, but had overall complication rates similar to smokers

Lung volume reduction surgery

3) **NETT 2003**, foundational trial of lung volume reduction surgery
    a) National Emphysema Treatment Trial (NETT)
        i) Inclusion criteria
            (a) Prerehabilitation plasma cotinine ≤13.7 ng/ml (if not using nicotine products) or prerehabilitation arterial carboxyhemoglobin ≤2.5% (if using nicotine products)
            (b) Nonsmoker (tobacco products) for 4 months prior to initial interview and patient remains a nonsmoker throughout screening (by history)
4) **Van Agterern 2015**, Cochrane review of lung volume reduction surgery
    a) All studies included in the review had smoking as an exclusion criteria

Erectile dysfunction surgery

No published literature was identified

Tobacco Cessation Requirements in Prioritized List Guidelines

Expert guidelines:

Spinal fusion

Lung volume reduction surgery

1) American Lung Association:
    a. Candidates for lung volume reduction surgery should "Have not smoked for at least six months"

Erectile dysfunction surgery

1) **American Urological Association 2018** guideline on erectile dysfunction
    a. Counseling on smoking cessation was recommended for all men with erectile dysfunction
    b. No mention of smoking cessation in their recommendations for any type of erectile dysfunction surgery

Other payer policies:

Spinal fusion

1) Aetna 2023
    a. For spinal fusion (cervical, lumbar and thoracic), the member should be nicotine-free (including smoking, use of tobacco products, and nicotine replacement therapy) for at least 6 weeks prior to surgery. For persons with recent nicotine use (unless there is evidence of spinal cord compression/myelopathy, cauda equina syndrome, severe weakness (graded 4 minus or less on MRC scale) or progressive weakness), documentation of nicotine cessation should include a lab report (not surgeon summary) showing blood nicotine level of less than or equal to 10 ng/ml, drawn within 6 weeks prior to surgery.
2) Cigna 2023
    a. For non-surgent spinal fusion surgery, Cigna requires a statement that the individual is a non-smoker or will refrain from use of tobacco products for at least six (6) weeks prior to the planned surgery.
3) Regence BCBS 2023
    a. The patient is not a tobacco user OR there is clinical documentation that the patient has been abstinent from tobacco use for at least six weeks prior to fusion
4) Washington Bureau of Labor and Industries
    a. abstain from nicotine for at least 4 weeks prior to surgery, as demonstrated by two negative urine cotinine tests during this time period. Abstinence from nicotine is required for all fusion and repeat fusion procedures.

Lung volume reduction surgery

1) CMS NCD for lung volume reduction surgery
    a. Tobacco related requirements:
        i. Plasma cotinine level ≤13.7 ng/mL (or arterial carboxyhemoglobin ≤ 2.5% if using nicotine products)
        ii. Nonsmoking for 4 months prior to initial interview and throughout evaluation for surgery
        iii. These requirements are the inclusion criteria for the NETT trial

Tobacco Cessation Requirements in Prioritized List Guidelines

Erectile dysfunction surgery

1) Aetna, Cigna, and Capital BCBS advise counseling on smoking cessation. Aetna requires no active smoking before vascular surgical interventions for ED. Cigna and Capital BCBS have no smoking cessation requirement before any ED procedure

Tobacco Cessation Requirements in Prioritized List Guidelines

HERC staff summary:

Spinal fusion: Smoking is consistently associated with lower fusion rates, with about 12.5% higher failure rate compared to non-smokers. Nicotine replacement therapy (NRT) has been shown to lead to higher fusion failure rates for lumbar fusions, but not for cervical fusions. All payers surveyed require at least 4 weeks of smoking cessation prior to spinal fusion, with the industry standard appearing to be 6 weeks. Most payers require cessation of NRT as well. Most require confirmatory cotinine testing (which would detect both smoking and NRT). HERC staff recommend reducing the requirement of abstinence from tobacco and NRT from 6 months down to 6 weeks in the spinal fusion guideline, and require only one negative cotinine test.

Lung volume reduction surgery: This surgery has never been studied in current smokers. All trials required smoking cessation. The foundational NETT trial allowed nicotine replacement, with a carboxyhemoglobin level test to prove abstinence from combustible cigarettes. This requirement is also contained in the CMS NCD regarding this surgery. HERC staff recommend removing the requirement for abstinence from all nicotine in the current guideline, as this is not consistent with the evidence. However, abstinence from combustible cigarettes should continue to be in the guideline, as all trials included this as a criteria; therefore, there is no evidence on the effectiveness of this surgery on current smokers.

Erectile dysfunction surgery: staff were unable to find published evidence on the impact of smoking on erectile dysfunction surgery outcomes. Smoking cessation is not mentioned in the expert guidelines on ED surgery and is not required by other payers surveyed. This guideline was added without any evidence review. HERC staff recommend deleting this guideline and allowing the general smoking and elective surgery statement of intent to be the only guidance.

HERC staff recommendations:

1) Modify GN 100 as shown below
    a. Reduce the period of abstinence to 6 weeks, reduce the required number of cotinine tests to one
2) Modify GN112 as shown below
    a. Changes requirement to the NETT study inclusion requirements/CMS NCD requirements
3) Delete GN159 as shown below

GUIDELINE NOTE 100, SMOKING AND SPINAL FUSION

Lines 47,150,200,254,346,361,401,478,530,559

Non-emergent spinal arthrodesis (CPT 22532-22634) is limited to patients who are non-smoking and abstinent from all nicotine products for 6 ~~months~~ weeks prior to the planned procedure, as shown by a negative cotinine urine or serum test ~~levels at least 6 months apart, with the second test within 1 month of the surgery date~~. Patients should be given access to appropriate smoking cessation therapy. Non-emergent spinal arthrodesis is defined as surgery for a patient with a lack of myelopathy or rapidly declining neurological exam.

Tobacco Cessation Requirements in Prioritized List Guidelines

GUIDELINE NOTE 112, LUNG VOLUME REDUCTION SURGERY

Line 283

Lung volume reduction surgery (LVRS, CPT 32491, 32672) is included on Line 283 only for treatment of patients with radiological evidence of severe bilateral upper lobe predominant emphysema (ICD-10-CM J43.9) and all of the following:

A) BMI ≤31.1 kg/m2 (men) or ≤32.3 kg/m 2 (women)
B) Stable with ≤20 mg prednisone (or equivalent) dose a day
C) Pulmonary function testing showing
    1) Forced expiratory volume in one second (FEV 1) ≤ 45% predicted and, if age 70 or older, FEV 1≥ 15% predicted value
    2) Total lung capacity (TLC) ≥ 100% predicted post-bronchodilator
    3) Residual volume (RV) ≥ 150% predicted post-bronchodilator
D) PCO_2, ≤ 60 mm Hg (PCO 2, ≤ 55 mm Hg if 1-mile above sea level)
E) PO_2, ≥ 45 mm Hg on room air (PO 2, ≥ 30 mm Hg if 1-mile above sea level)
F) Post-rehabilitation 6-min walk of ≥ 140 m
~~G) Non-smoking and abstinence from all nicotine products for 6 months prior to surgery, as shown by negative cotinine levels at least 6 months apart, with the second test within 1 month of the surgery date.~~
H) Non-smoking for 4 months prior to initial surgical evaluation and throughout the pre-surgical process
    1) This must be demonstrated by a negative serum or urine cotinine level (if not using nicotine replacement products), or an arterial carboxyhemoglobin ≤ 2.5% if using nicotine replacement) prior to surgical authorization

The procedure must be performed at an approved facility (1) certified by the Joint Commission on Accreditation of Healthcare Organizations (Joint Commission) under the LVRS Disease Specific Care Certification Program or (2) approved as Medicare lung or heart-lung transplantation hospitals. The patient must have approval for surgery by pulmonary physician, thoracic surgeon, and anesthesiologist post-rehabilitation. The patient must have approval for surgery by cardiologist if any of the following are present: unstable angina; left-ventricular ejection fraction (LVEF) cannot be estimated from the echocardiogram; LVEF <45%; dobutamine-radionuclide cardiac scan indicates coronary artery disease or ventricular dysfunction; arrhythmia (>5 premature ventricular contractions per minute; cardiac rhythm other than sinus; premature ventricular contractions on EKG at rest).

~~GUIDELINE NOTE 159, SMOKING AND SURGICAL TREATMENT OF ERECTILE DYSFUNCTION~~

~~*Line 523*~~

~~Surgical treatment of erectile dysfunction is only included on this line when patients are non-smoking and abstinent from all nicotine products for 6 months prior to surgery, as shown by negative cotinine levels at least 6 months apart, with the second test within 1 month of the surgery date~~

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The Risk of Nonunion in Smokers Revisited: A Systematic Review and Meta-Analysis

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Abstract

Study Design: Systemic review and meta-analysis.

Objective: To review and establish the effect of tobacco smoking on risk of nonunion following spinal fusion.

Methods: A systematic search of Medline, Embase, Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews from inception to December 31, 2020, was conducted. Cohort studies directly comparing smokers with nonsmokers that provided the number of nonunions and fused segments were included. Following data extraction, the risk of bias was assessed using the Quality in Prognosis Studies Tool, and the strength of evidence for nonunion was evaluated using the GRADE working group criteria. All data analysis was performed in Review Manager 5, and a random effects model was used.

Results: Twenty studies assessing 3009 participants, which included 1117 (37%) smokers, met inclusion criteria. Pooled analysis found that smoking was associated with increased risk of nonunion compared to not smoking ≥1 year following spine surgery (RR 1.91, 95% CI 1.56 to 2.35). Smoking was significantly associated with increased nonunion in those receiving either allograft (RR 1.39, 95% CI 1.12 to 1.73) or autograft (RR 2.04, 95% CI 1.54 to 2.72). Both multilevel and single level fusions carried increased risk of nonunion in smokers (RR 2.30, 95% CI 1.64 to 3.23; RR 1.79, 95% CI 1.12 to 2.86, respectively).

Conclusion: Smoking status carried a global risk of nonunion for spinal fusion procedures regardless of follow-up time, location, number of segments fused, or grafting material. Further comparative studies with robust methodology are necessary to establish treatment guidelines tailored to smokers.

Keywords

smoking, nicotine, tobacco, fusion, nonunion, pseudarthrosis, meta-analysis, systematic review

Background

Tobacco use remains a global public health problem in the 21st century. In the United States alone, cigarette smoking remains the leading cause of preventable disease, disability, and death, accounting for nearly 500,000 annual deaths or 1 in 5 of all deaths.[1] Health policy strategies and pharmacologic interventions have demonstrated only partial effectiveness in mitigating rates of tobacco use.[2,3] The wide-ranging negative impact of smoking on outcomes after surgical procedures in

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The Effect of Smoking on the Fusion Rate of Spinal Fusion Surgery: A Systematic Review and Meta-Analysis

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OBJECTIVE: **To conduct a systematic review and meta-analysis comparing the fusion rate after spinal fusion surgery between smokers and nonsmokers.**

METHODS: **We searched PubMed, Embase, Cochrane Library, and Web of Science electronic databases through March 10, 2021 for cohort and case–control studies assessing the effect of smoking on the fusion rate of spinal fusion surgery. Two researchers independently screened the literature and extracted data according to the inclusion and exclusion criteria. Statistical analysis was performed using RevMan, version 5.4.**

RESULTS: **A total of 26 studies, including 4 case–control studies and 22 cohort studies, with 4409 patients, were included in the present meta-analysis. Follow-up was at least 6 months. Overall, the pooled results demonstrated that the fusion rate of smokers after spinal fusion was significantly lower than that of nonsmokers. The odds ratio (OR) was 0.55 (95% confidence interval [CI] 0.45–0.67, $P < 0.0001$). Subgroup analyses by fusion level showed the adverse effect of smoking on the fusion rate at single level (OR 0.61, 95% CI 0.41–0.91, $P = 0.02$) was more significant than that of multiple levels (OR 0.55, 95% CI 0.38–0.80, $P = 0.0010$). Subgroup analysis according to the type of bone graft revealed an apparent association between smoking and fusion rate in the autograft subgroup (OR 0.47, 95% CI 0.33–0.66, $P < 0.0001$) but not in the allograft subgroup (OR 0.69, 95% CI 0.47–1.01, $P = 0.06$).**

CONCLUSIONS: **The fusion rate of smokers is significantly lower than that of nonsmokers in spinal fusion surgery. Smokers should be encouraged to quit smoking to improve the outcome of spinal fusion surgery.**

INTRODUCTION

Pseudarthrosis, or failure of bony union, is a well-known complication of spinal fusion, which can lead to migration or breakage of implants and loosening of pedicle screws. Further development of the pseudarthrosis may cause spinal instability, which may worsen clinical outcomes.[1,2] It has been reported that the rates of pseudoarthrosis or fusion failure are as high as 40 % in primary spinal fusion surgery and up to 60 % in revision cases.[3,4] It is important to identify variables that may increase the risk of spinal fusion failure so that strategies can be developed to reduce the risk of spinal fusion failure.

Smoking has many health risks and complications that are not only well documented in the cardiovascular and respiratory systems, but emerging literature suggests that smoking is also associated with adverse surgical outcomes, including wound infection, sepsis, and delayed healing.[5-7] Compared with nonsmokers, smokers who undergo surgery have longer hospital stay, greater risk of readmission, and greater risk of in-hospital death.[8-10]

Several studies have examined the relationship between smoking and fusion rates for spinal fusion surgery in recent decades. However, controversy regarding whether smoking increases the rate of spinal fusion failure still exists. Some studies found no association,[11,12] whereas some observed that smoking had a significant effect on the rate of spinal fusion.[13,14] The difference

Key words
- Fusion rate
- Meta-analysis
- Smoking
- Spinal fusion

Abbreviations and Acronyms
ACDF: Anterior cervical discectomy and fusion
CI: Confidence interval
CT: Computed tomography
NOS: Newcastle-Ottawa Scale
OR: Odds ratio

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The Impact of Smoking Cessation Therapy on Lumbar Fusion Outcomes

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■ OBJECTIVE: **While there are several reports on the impact of smoking tobacco on spinal fusion outcomes, there is minimal literature on the influence of modern smoking cessation therapies on such outcomes. Our study explores the outcomes of single-level lumbar fusion surgery in active smokers and in smokers undergoing recent cessation therapy.**

■ METHODS: **MARINER30, an all-payer claims database, was utilized to identify patients undergoing single-level lumbar fusions between 2010 and 2019. The primary outcomes were the rates of any complication, symptomatic pseudarthrosis, need for revision surgery, and all-cause readmission within 30 and 90 days.**

■ RESULTS: **The exact matched population analyzed in this study contained 31,935 patients undergoing single-level lumbar fusion with 10,645 (33%) in each of the following groups: (1) active smokers; (2) patients on smoking cessation therapy; and (3) those without any smoking history. Patients undergoing smoking cessation therapy have reduced odds of developing any complication following surgery (odds ratio 0.86, 95% confidence interval 0.80—0.93) when compared with actively smoking patients. Nonsmokers and patients on cessation therapy had a significantly lower rate of any complication compared with the smoking group (9.5% vs. 17% vs. 19%, respectively).**

■ CONCLUSIONS: **When compared with active smoking, preoperative smoking cessation therapy within 90 days of surgery decreases the likelihood of all-cause postoperative complications. However, there were no between-group differences in the likelihood of pseudarthrosis, revision surgery, or readmission within 90 days.**

INTRODUCTION

It is known that smoking tobacco has negative molecular effects on bone health.[1-3] Specifically, impairment of angiogenesis, osteoblast interference, mediation of inflammatory processes, and reduced gene expression of beneficial signaling molecules contribute to poor bone healing,[4-7] supporting the increased likelihood of nonunion following fusion surgery.[3] To combat the well-documented, negative effects of tobacco on surgical outcomes, there has been a widespread encouragement of preoperative smoking cessation programs across the country.[8] Although there are several reports on the impact of smoking tobacco on spinal fusion outcomes, [9-14] there is minimal literature on the influence of modern cessation therapies, such as nicotine replacement therapy (NRT), on spinal fusion outcomes. Consequently, understanding how smoking cessation products such as NRT affect outcomes is important for preoperative risk stratification and enhanced informed consent. To this end, we sought to explore the effects of smoking cessation therapies on spinal fusion outcomes.

METHODS

Data Source

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Key words
- Arthrodesis
- Lumbar vertebrae
- Nicotine
- Spine
- Tobacco use cessation devices
- Tobacco products

Abbreviations and Acronyms
CI: Confidence Interval
CM: Clinical Modification
CPT: Current Procedural Terminology
ICD: International Classifications of Diseases
NRT: Nicotine Replacement Therapy
OR: Odds Ratio

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The impact of smoking and smoking cessation interventions on outcomes following single-level anterior cervical discectomy and fusion procedures☆

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ABSTRACT

Background: While several studies explore the impact of smoking tobacco on spinal fusion outcomes, there is a paucity of literature on the influence of modern smoking cessation therapies on such outcomes in patients undergoing anterior cervical discectomy and fusion (ACDF).
Objective: Our study explores the outcomes of single-level ACDF surgery in nonsmokers, active smokers, and smokers undergoing cessation therapy.
Methods: MARINER30, an all-payer claims database, was utilized to identify patients undergoing single-level ACDF between 2010 and 2019. The primary outcomes were the rates of composite surgical complications, dysphagia, hematoma, symptomatic pseudarthrosis, instrumentation removal, need for revision surgery, and all-cause readmission rates within 30 and 90-days.
Results: The matched population consisted of 5769 patients undergoing single-level ACDF with 1923 (33.33%) in each of the following groups: (1) nonsmokers; (2) active smokers; and (3) patients undergoing smoking cessation therapy. Nonsmokers had significantly lower rates of composite surgical complications (3.74% vs 13.05% vs 15.08%), revision surgery (4.06% vs 20.07% vs 22.88%), instrumentation removal (0.83% vs. 2.08% vs. 2.76%), and dysphagia (0.36% vs 0.99% vs 0.62%) when compared to patients in the active smoking and smoking cessation groups, respectively.
Conclusion: Patients using smoking cessation therapy were more likely to develop postoperative dysphagia and undergo revision surgery when compared to their actively smoking counterparts. While surgeons routinely recommend smoking cessation prior to surgery, the effects of smoking cessation therapies on surgical outcomes are not well characterized.

1. Introduction

Extensive research has demonstrated that smoking tobacco has detrimental molecular effects on bone health [1–6]. Specifically, smoking tobacco is associated with impairment of angiogenesis, interference of osteoblast activity, mediation of inflammatory processes, and reduced gene expression of signaling molecules beneficial to bone healing, [2,7,8]. likely explaining the increased incidence of nonunion in smokers undergoing spinal fusion surgery.9 As a result of the well-documented, negative effects of smoking tobacco on surgical outcomes, surgeons across the country are increasingly encouraging smoking cessation programs as an integral part of preoperative medical optimization [9]. Although several studies have investigated the effect of smoking tobacco on spinal fusion outcomes, [10–14] there is a lack of literature examining the effectiveness of modern cessation therapies, such as nicotine replacement therapy (NRT), on anterior cervical discectomy and fusion (ACDF) outcomes. To this end, the present study explores the effects of smoking cessation therapies on outcomes

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A Randomized Trial Comparing Lung-Volume–Reduction Surgery with Medical Therapy for Severe Emphysema

National Emphysema Treatment Trial Research Group*

ABSTRACT

BACKGROUND

Lung-volume–reduction surgery has been proposed as a palliative treatment for severe emphysema. Effects on mortality, the magnitude and durability of benefits, and criteria for the selection of patients have not been established.

METHODS

A total of 1218 patients with severe emphysema underwent pulmonary rehabilitation and were randomly assigned to undergo lung-volume–reduction surgery or to receive continued medical treatment.

RESULTS

Overall mortality was 0.11 death per person-year in both treatment groups (risk ratio for death in the surgery group, 1.01; P=0.90). After 24 months, exercise capacity had improved by more than 10 W in 15 percent of the patients in the surgery group, as compared with 3 percent of patients in the medical-therapy group (P<0.001). With the exclusion of a subgroup of 140 patients at high risk for death from surgery according to an interim analysis, overall mortality in the surgery group was 0.09 death per person-year, as compared with 0.10 death per person-year in the medical-therapy group (risk ratio, 0.89; P=0.31); exercise capacity after 24 months had improved by more than 10 W in 16 percent of patients in the surgery group, as compared with 3 percent of patients in the medical-therapy group (P<0.001). Among patients with predominantly upper-lobe emphysema and low exercise capacity, mortality was lower in the surgery group than in the medical-therapy group (risk ratio for death, 0.47; P=0.005). Among patients with non–upper-lobe emphysema and high exercise capacity, mortality was higher in the surgery group than in the medical-therapy group (risk ratio, 2.06; P=0.02).

CONCLUSIONS

Overall, lung-volume–reduction surgery increases the chance of improved exercise capacity but does not confer a survival advantage over medical therapy. It does yield a survival advantage for patients with both predominantly upper-lobe emphysema and low base-line exercise capacity. Patients previously reported to be at high risk and those with non–upper-lobe emphysema and high base-line exercise capacity are poor candidates for lung-volume–reduction surgery, because of increased mortality and negligible functional gain.

The writing committee for the National Emphysema Treatment Trial (NETT) (Alfred Fishman, M.D., University of Pennsylvania, Philadelphia; Fernando Martinez, M.D., University of Michigan, Ann Arbor; Keith Naunheim, M.D., Saint Louis University, St. Louis; Steven Piantadosi, M.D., Ph.D., and Robert Wise, M.D., Johns Hopkins University, Baltimore; Andrew Ries, M.D., M.P.H., University of California, San Diego, La Jolla; Gail Weinmann, M.D., National Heart, Lung, and Blood Institute, Bethesda, Md.; and Douglas E. Wood, M.D., University of Washington, Seattle) takes responsibility for the content of this article. Address reprint requests to Dr. Piantadosi at the NETT Coordinating Center, 615 N. Wolfe St., Rm. 5010, Baltimore, MD 21205.

*The members of the National Emphysema Treatment Trial Research Group are listed in the Appendix.

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: National Emphysema Treatment Trial Research Group. A Randomized Trial Comparing Lung-Volume–Reduction Surgery with Medical Therapy for Severe Emphysema. N Engl J Med 2003; 348:2059-73.

Supplementary Appendix 1. Criteria for Inclusion and Exclusion.*

Inclusion criteria

History and physical exam consistent with emphysema

CT scan evidence of bilateral emphysema

Prerehabilitation postbronchodilator TLC ≥100% predicted

Prerehabilitation postbronchodilator RV ≥150% predicted

Prerehabilitation FEV_1 (maximum of pre- and postbronchodilator values) ≤45% of predicted and, if age ≥70 years prerehabilitation, FEV_1 (maximum of pre- and postbronchodilator values) ≥15% of predicted

Prerehabilitation room air, resting $PaCO_2$ ≤60 mm Hg (≤55 mm Hg in Denver)

Prerehabilitation room air, resting PaO_2 ≥45 mm Hg (≥30 mm Hg in Denver)

Prerehabilitation plasma cotinine ≤13.7 ng/ml (if not using nicotine products) or prerehabilitation arterial carboxyhemoglobin ≤2.5% (if using nicotine products)

Body-mass index ≤31.1 (males) or ≤32.3 (females) as of randomization

Nonsmoker (tobacco products) for 4 months prior to initial interview and patient remains a nonsmoker throughout screening (by history)

Approval for surgery by cardiologist if any of the following findings are noted prior to randomization (approval must be obtained prior to randomization):

- Unstable angina
- Left ventricular ejection fraction cannot be estimated from the echocardiogram
- Left ventricular ejection fraction <45%
- Dobutamine-radionuclide cardiac scan indicates coronary artery disease or ventricular dysfunction
- >5 premature ventricular beats/minute (does not apply during exercise testing)
- Cardiac rhythm other than sinus or premature atrial contractions noted during resting EKG
- S_3 gallop on physical examination

Completion of all prerehabilitation assessments

Judgment by study physician that patient is likely to be approved for surgery upon completion of the rehabilitation program

Completion of NETT rehabilitation program

Completion of all postrehabilitation and all randomization assessments

Approval for surgery by pulmonary physician and thoracic surgeon in consultation with the anesthesiologist, postrehabilitation and just prior to randomization

Consent

Supplementary Appendix 1. (Continued.)

Exclusion criteria

Postrehabilitation, postbronchodilator FEV_1 ≤20% predicted and either nonheterogeneous emphysema on CT scan or D_LCO ≤20% predicted (enacted May 2001)

Inability to provide a valid D_LCO measurement (enacted May 2001)

CT scan evidence of diffuse emphysema judged unsuitable for LVRS

Previous lung volume reduction surgery (laser or excision)

Pleural or interstitial disease which precludes surgery

Giant bulla (≥⅓ of the volume of the lung in which the bulla is located)

Clinically significant bronchiectasis

Pulmonary nodule requiring surgery

Previous sternotomy or lobectomy

Myocardial infarction within 6 months of interview and ejection fraction <45%

Congestive heart failure within 6 months of interview and ejection fraction <45%

Uncontrolled hypertension (systolic >200 mm Hg or diastolic >110 mm Hg)

Pulmonary hypertension: mean P_{PA} on right heart catheterization ≥35 mm Hg (≥38 mm Hg in Denver) or peak systolic P_{PA} on right heart catheterization ≥45 mm Hg (≥50 mm Hg in Denver); right heart catheterization is required to rule out pulmonary hypertension if peak systolic P_{PA} on echocardiogram >45 mm Hg

Unplanned, unexplained weight loss >10% usual weight in 90 days prior to interview or unplanned, explained weight loss >10% usual weight in 90 days prior to interview that is judged likely to interfere with completion of the trial

History of recurrent infections with daily sputum production judged clinically significant

Daily use of more than 20 mg of prednisone or its equivalent as of randomization

History of exercise-related syncope

Resting bradycardia (<50 beats/min), frequent multifocal PVCs, or complex ventricular arrhythmia or sustained SVT

Other cardiac dysrhythmia which, in the judgment of the supervising physician, might pose a risk to the patient during exercise testing or training

Oxygen requirement during resting or Part 1 oxygen titration exceeding 6 L/min to keep saturation ≥90%

Evidence of systemic disease or neoplasia that is expected to compromise survival over the duration of the trial

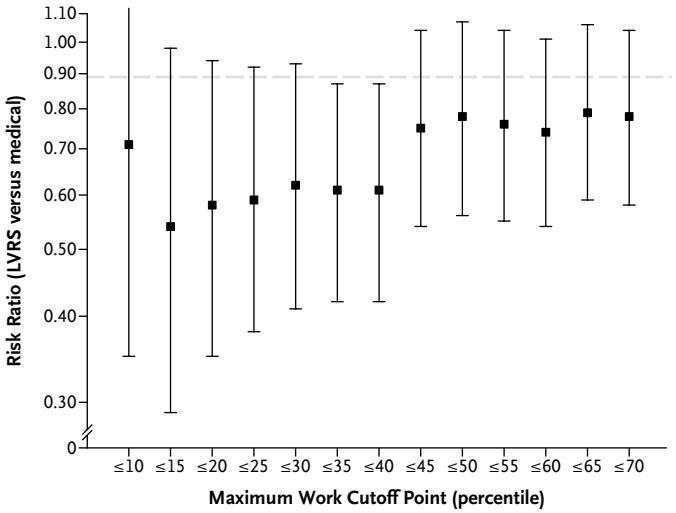
Any disease or condition which may interfere with completion of tests, therapy, or follow-up

Six-minute walk distance ≤140 m postrehabilitation

Inability to complete successfully any of the screening or base-line data collection procedures (e.g., hypoxemia to SpO_2 <80% within 2 minutes of unloaded pedaling despite supplemental oxygen, inability to coordinate a regular cadence of >40 cpm, inability to complete 3 minutes unloaded pedaling, claudication, lower extremity or back orthopedic problems that prohibit sustained pedaling)

* CT denotes computed tomography, TLC total lung capacity, FEV_1 forced expiratory volume in one second, $PaCO_2$ partial pressure of arterial carbon dioxide, PaO_2 partial pressure of arterial oxygen, EKG electrocardiogram, D_LCO carbon monoxide diffusing capacity, LVRS lung-volume–reduction surgery, P_{PA} pulmonary-artery pressure, PVC premature ventricular contraction, SVT supraventricular tachycardia, and SpO_2 oxygen saturation by pulse oximetry. The body-mass index is the weight in kilograms divided by the square of the height in meters.

Supplement to National Emphysema Treatment Trial Research Group. A Randomized Trial Comparing Lung-Volume–Reduction Surgery with Medical Therapy for Severe Emphysema. N Engl J Med 2003;348:2059-73.



Supplementary Appendix 2. Sensitivity Analysis of Sex-Specific Cutoff Points for Subgroups Defined According to Maximal Workload.

Graph shows the risk ratio (lung-volume–reduction surgery [LVRS] vs. medical therapy) for percentile cutoff points of base-line maximal workload, ranging from the 10th percentile to the 70th percentile in 5-percentile steps. The cutoff points for a given patient vary according to sex; for example, the 40th percentile for base-line maximal workload for women was 25 W, whereas the 40th percentile for men was 40 W. This graph suggests the 40th percentile of base-line maximal workload as the cutoff point beyond which the risk ratio increases.

Supplementary Appendix 3. Postrehabilitation Base-Line Characteristics of Non–High-Risk Patients.*

Characteristic	All Non–High-Risk Patients		Patients with Upper-Lobe Predominance				Patients with Non–Upper-Lobe Predominance			
	Surgery (N=538)	Medical Therapy (N=540)	Surgery, Low Exercise Capacity (N=139)	Medical Therapy, Low Exercise Capacity (N=151)	Surgery, High Exercise Capacity (N=206)	Medical Therapy, High Exercise Capacity (N=213)	Surgery, Low Exercise Capacity (N=84)	Medical Therapy, Low Exercise Capacity (N=65)	Surgery, High Exercise Capacity (N=109)	Medical Therapy, High Exercise Capacity (N=111)
Age at randomization — yr	67.0±6.2	67.1±5.8	67.2±5.2	67.6±5.4	66.6±6.4	66.5±5.6	67.4±6.7	69.0±5.5	67.3±6.4	66.4±6.6
Race or ethnic group — no. (%)										
Non-Hispanic white	513 (95)	511 (95)	130 (94)	142 (94)	199 (97)	201 (94)	77 (92)	61 (94)	107 (98)	107 (96)
Non-Hispanic black	17 (3)	18 (3)	7 (5)	5 (3)	2 (1)	7 (3)	7 (8)	4 (6)	1 (1)	2 (2)
Other	8 (1)	11 (2)	2 (1)	4 (3)	5 (2)	5 (2)	0 (0)	0 (0)	1 (1)	2 (2)
Sex — no. (%)†										
Female	235 (44)	200 (37)	63 (45)	51 (34)	88 (43)	85 (40)	38 (45)	25 (38)	46 (42)	39 (35)
Male	303 (56)	340 (63)	76 (55)	100 (66)	118 (57)	128 (60)	46 (55)	40 (62)	63 (58)	72 (65)
Distribution of emphysema on CT — no. (%)‡										
Upper-lobe predominance	345 (64)	364 (67)	139 (100)	151 (100)	206 (100)	213 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Non–upper-lobe predominance	193 (36)	176 (33)	0 (0)	0 (0)	0 (0)	0 (0)	84 (100)	65 (100)	109 (100)	111 (100)
Heterogeneous	306 (57)	314 (58)	103 (74)	110 (73)	147 (71)	144 (68)	27 (32)	21 (32)	29 (27)	39 (35)
Homogeneous	232 (43)	226 (42)	36 (26)	41 (27)	59 (29)	69 (32)	57 (68)	44 (68)	80 (73)	72 (65)
Perfusion ratio§	0.30±0.22	0.29±0.23	0.23±0.13	0.20±0.11	0.23±0.14	0.22±0.12	0.48±0.34	0.40±0.20	0.40±0.19	0.47±0.37
Maximal workload — W	40.0±21.1	41.3±22.3	22.4±11.5	22.8±11.8	51.2±17.8	52.5±19.1	25.0±9.7	23.3±9.4	53.2±19.9	56.2±19.3
Distance walked in 6 min — ft	1239.4± 307.5	1247.8± 309.9	1075.2± 277.1	1058.4± 244.0	1352.9± 280.9	1346.0± 289.1	1112.7± 275.7	1075.8± 272.4	1332.1± 288.9	1417.7± 265.7
FEV_1 after bronchodilator use — % of predicted value	28.1±6.8	27.9±6.5	25.4±6.8	25.2±6.1	29.5±6.5	29.1±6.6	25.9±5.9	26.6±6.0	30.7±6.4	30.0±5.7
Total lung capacity after bronchodilator use — % of predicted value	127.4±15.0	127.6±14.1	128.0±14.1	127.2±15.3	125.1±14.3	126.6±13.5	130.7±17.8	131.6±15.9	128.4±14.8	127.6±12.1
Residual volume after bronchodilator use — % of predicted value	214.4±45.6	216.7±43.8	223.5±43.3	226.0±48.2	206.6±42.0	210.2±39.2	227.9±57.4	226.3±45.7	207.2±40.5	211.1±42.0
Carbon monoxide diffusing capacity — % of predicted value	29.2±9.3	29.4±9.5	26.0±8.5	26.0±8.4	31.2±8.4	31.0±9.3	27.0±9.3	26.8±9.0	31.3±10.5	32.7±9.7
PaO_2 — mm Hg	65.0±10.6	64.8±10.1	63.8±10.0	63.6±10.5	66.1±10.7	66.2±9.7	63.6±11.7	63.3±10.0	65.7±10.1	64.7±10.2
$PaCO_2$ — mm Hg	42.8±5.7	42.4±5.5	43.9±6.2	43.2±5.7	42.6±5.8	42.5±5.6	42.6±5.8	42.8±5.2	42.1±4.6	41.1±5.1
St. George's Respiratory total score¶	52.2±12.8	53.2±12.8	54.3±12.1	57.0±12.4	51.2±12.5	50.8±12.5	56.2±13.2	55.5±12.8	48.1±12.6	51.4±12.8
Quality of Well-Being average daily score‖	0.58±0.12	0.57±0.11	0.57±0.12	0.54±0.12	0.59±0.12	0.58±0.11	0.56±0.11	0.55±0.11	0.60±0.11	0.59±0.11
UCSD Shortness of Breath total score**	60.7±18.3	62.3±18.8	64.5±16.9	71.0±15.9	59.0±17.7	57.1±18.6	68.3±17.7	68.5±17.2	53.3±18.2	56.8±18.1

* Base-line measurements were obtained after rehabilitation but before randomization, except for carbon monoxide diffusing capacity, which was obtained before rehabilitation. Plus–minus values are means ±SD. High-risk patients were defined as those with a forced expiratory volume in one second (FEV_1) that was 20 percent or less of the predicted value and either homogeneous emphysema or a carbon monoxide diffusing capacity that was 20 percent or less of the predicted value. CT denotes computed tomography, PaO_2 the partial pressure of arterial oxygen, and $PaCO_2$ the partial pressure of arterial carbon dioxide.

† Among non–high-risk patients, P for homogeneity=0.03. Among patients with upper-lobe predominance and low exercise capacity, P for homogeneity=0.04.

‡ Upper-lobe predominance of emphysema was judged subjectively by each center's radiologist; choices were upper-lobe predominance, lower-lobe predominance, diffuse, or superior segments of lower lobes predominantly involved; the latter three choices were grouped as non–upper-lobe predominance. The heterogeneity of the emphysema was based on subjective scores assigned by each center's radiologist to each of three zones in each lung.

§ The perfusion ratio was derived from the radionuclide perfusion scan. Each lung is divided into three zones; a percentage of total perfusion is assigned to each zone. The ratio is calculated as the sum of the percentages assigned to the two upper zones divided by the sum of the percentages assigned to the four middle and lower zones.

¶ The St. George's Respiratory Questionnaire is a 51-item health-related quality-of-life questionnaire about respiratory symptoms that is completed by the patient; the total score ranges from 0 to 100, and lower scores indicate better health-related quality of life.

‖ The Quality of Well-Being scale is a 77-item questionnaire on quality of life that is completed by the patient. The average daily total score ranges from 0 to 1, with higher scores indicating better quality of life.

** The UCSD Shortness of Breath Questionnaire is a 24-item questionnaire on shortness of breath (dyspnea) that is completed by the patient; the total score ranges from 0 to 120, and lower scores indicate less shortness of breath.

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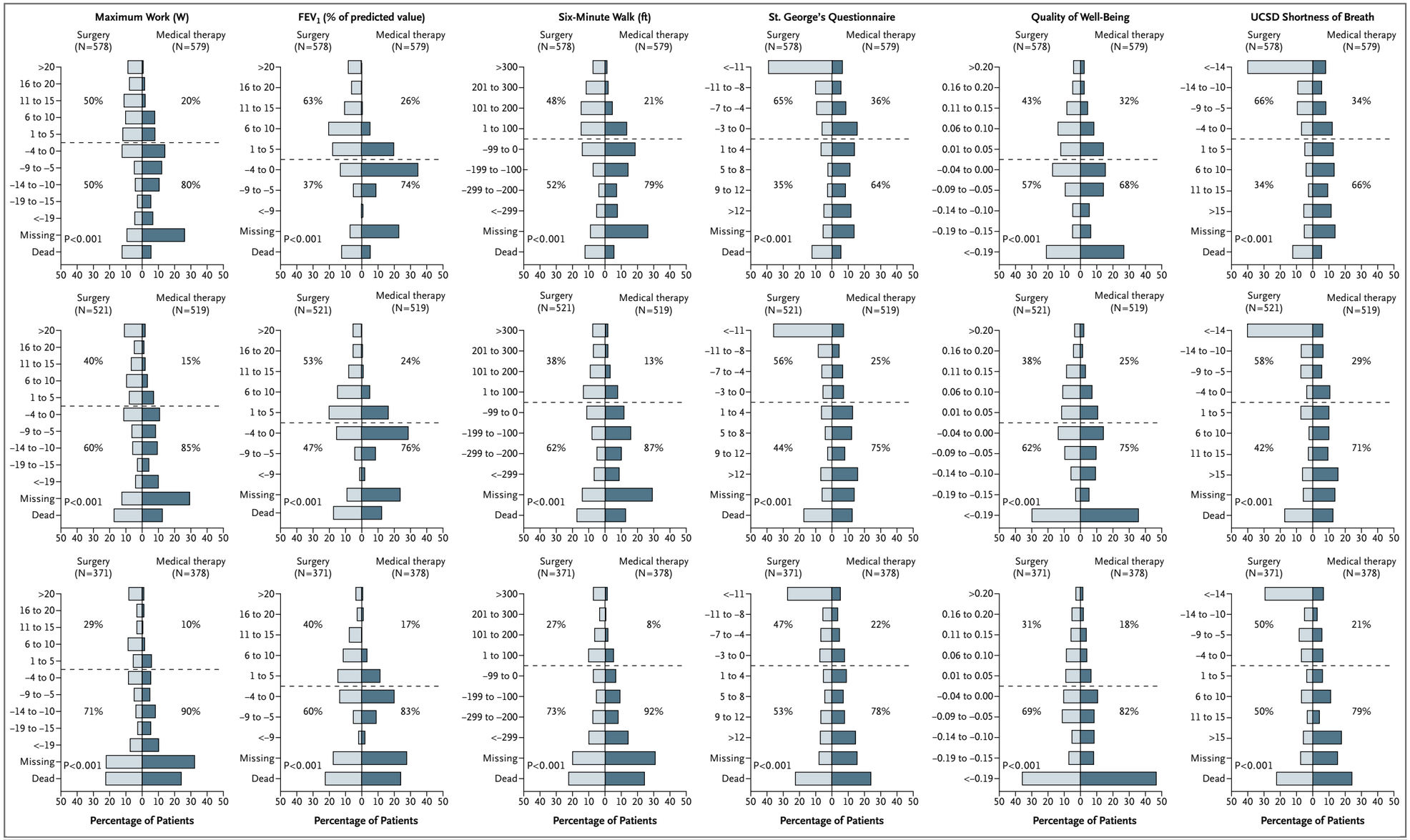


Supplementary Appendix 4. Histograms of Changes from Postrehabilitation Base Line in Exercise Capacity (Maximal Workload), Percentage of Predicted Value for Forced Expiratory Volume in One Second (FEV_1), Distance Walked in Six Minutes, Health-Related Quality of Life (St. George's Respiratory Questionnaire), Quality of Life (Quality of Well-Being Scale), and Dyspnea (UCSD Shortness of Breath Questionnaire) after 6, 12, and 24 Months of Follow-up.

The category "missing" includes patients who were too ill to complete the procedure or who declined to complete the procedure but did not explain why. For the Quality of Well-Being scale, patients who died were assigned a score of 0 on the questionnaire for the visit, and patients who did not complete the questionnaire were assigned a score equal to half of the lowest score observed for the visit. P values were determined by the Wilcoxon rank-sum test. The degree to which the bars are shifted to the upper left of the chart indicates the degree of a relative benefit of lung-volume–reduction surgery (LVRS) over medical treatment. The percentage shown in each quadrant is the percentage of patients in the specified treatment group with a change in the outcome falling into that quadrant. This was an intention-to-treat analysis.

Supplement to National Emphysema Treatment Trial Research Group. A Randomized Trial Comparing Lung-Volume–Reduction Surgery with Medical Therapy for Severe Emphysema. N Engl J Med 2003;348:2059-73.

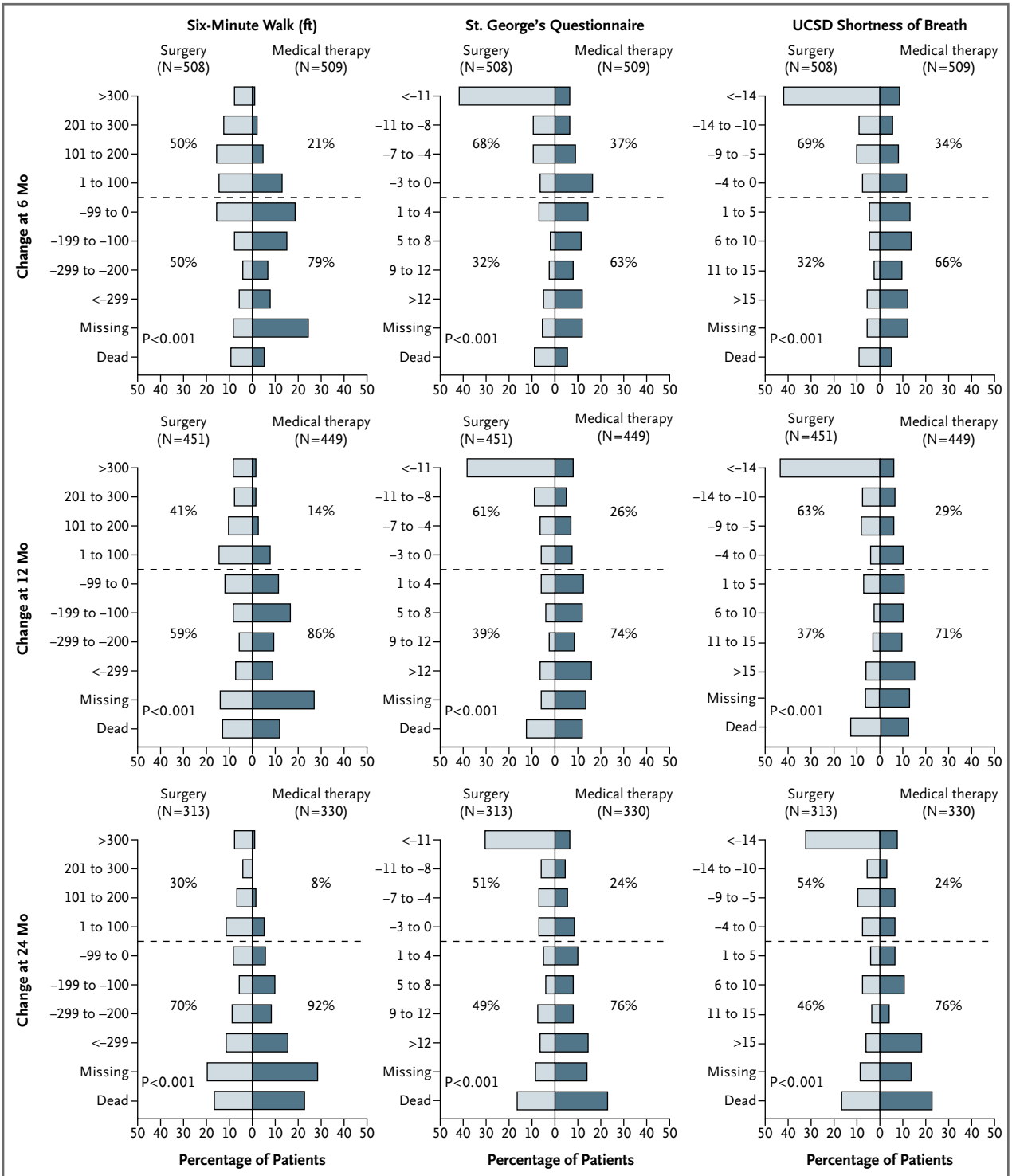
Supplementary Appendix 5. **Patient's Place of Residence According to the Time since Randomization.***

Variable	All Patients		Non–High-Risk Patients		Upper-Lobe Predominance, Low Exercise Capacity		Upper-Lobe Predominance, High Exercise Capacity		Non–Upper-Lobe Predominance, Low Exercise Capacity		Non–Upper-Lobe Predominance, High Exercise Capacity	
	Surgery	Medical Therapy	Surgery	Medical Therapy	Surgery	Medical Therapy	Surgery	Medical Therapy	Surgery	Medical Therapy	Surgery	Medical Therapy
1 Mo												
Private home (%)	66.8	97.5	69.7	97.6	65.5	97.4	74.3	96.7	66.7	100	68.8	98.2
Nursing home or rehabilitation facility (%)	0.7	0	0.6	0	0.7	0	0.5	0	1.2	0	0	0
Acute care hospital (%)	24.0	0.3	23.1	0.4	29.5	0.7	19.4	0.5	21.4	0	22.9	0
Living, no data (%)	4.9	2.0	4.5	1.9	2.9	2.0	3.9	2.8	7.1	0	5.5	0.9
Dead (%)	3.6	0.2	2.2	0.2	1.4	0	1.9	0	3.6	0	2.8	0.9
No. of patients	608	610	538	540	139	151	206	213	84	65	109	111
P value	<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
Median time since surgery (mo)	0.7		0.7		0.8		0.7		0.8		0.7	
2 Mo												
Private home (%)	78.3	96.1	80.9	95.9	77.0	93.4	83.0	96.2	78.6	98.5	83.5	97.3
Nursing home or rehabilitation facility (%)	0.7	0.2	0.7	0.2	2.2	0	0	0.5	1.2	0	0	0
Acute care hospital (%)	8.4	0.3	8.6	0.2	13.0	0	8.7	0	7.1	1.5	3.7	0
Living, no data (%)	5.8	2.8	5.0	3.0	5.0	4.6	5.8	3.3	6.0	0	2.8	1.8
Dead (%)	6.9	0.7	4.8	0.7	2.9	2.0	2.4	0	7.1	0	10.1	0.9
No. of patients	608	610	538	540	139	151	206	213	84	65	109	111
P value	<0.001		<0.001		<0.001		<0.001		<0.001		0.001	
Median time since surgery (mo)	1.7		1.7		1.8		1.7		1.7		1.7	
4 Mo												
Private home (%)	84.5	94.3	87.7	94.6	90.7	91.4	90.3	95.3	79.8	98.5	85.3	95.5
Nursing home or rehabilitation facility (%)	0.8	0.2	0.9	0.2	1.4	0.7	0.5	0	2.4	0	0	0
Acute care hospital (%)	1.8	0.5	2.0	0.6	2.9	0	1.5	0.5	3.6	0	0.9	1.8
Living, no data (%)	4.4	2.8	3.7	2.4	2.2	4.0	3.9	2.4	6.0	0	3.7	1.8
Dead (%)	8.4	2.3	5.6	2.2	2.9	4.0	3.9	1.9	8.3	1.5	10.1	0.9
No. of patients	608	610	538	540	139	151	206	213	84	65	109	111
P value	<0.001		<0.001		0.89		0.05		0.001		0.008	
Median time since surgery (mo)	3.7		3.7		3.7		3.6		3.6		3.7	

Supplementary Appendix 5. (Continued.)

Variable	All Patients		Non–High-Risk Patients		Upper-Lobe Predominance, Low Exercise Capacity		Upper-Lobe Predominance, High Exercise Capacity		Non–Upper-Lobe Predominance, Low Exercise Capacity		Non–Upper-Lobe Predominance, High Exercise Capacity	
	Surgery	Medical Therapy	Surgery	Medical Therapy	Surgery	Medical Therapy	Surgery	Medical Therapy	Surgery	Medical Therapy	Surgery	Medical Therapy
8 Mo												
Private home (%)	85.3	90.9	88.6	91.2	89.5	84.8	91.2	94.0	86.4	89.2	84.5	96.0
Nursing home or rehabilitation facility (%)	0.5	0.2	0.6	0.2	1.5	0.7	0	0	1.2	0	0	0
Acute care hospital (%)	0.7	0.5	0.8	0.4	0.8	0	0.5	1.0	1.2	0	1.0	0
Living, no data (%)	2.2	3.1	2.0	3.1	3.0	4.8	2.6	2.5	0	3.1	1.0	2.0
Dead (%)	11.2	5.3	8.0	5.1	5.3	9.7	5.7	2.5	11.1	7.7	13.6	2.0
No. of patients	580	582	510	512	133	145	193	201	81	65	103	101
P value	0.002		0.16		0.22		0.26		0.60		0.005	
Median time since surgery (mo)	7.7		7.8		7.7		7.8		7.7		7.7	
18 Mo												
Private home (%)	78.4	83.8	83.0	84.3	87.3	77.2	84.4	90.9	76.7	74.1	80.0	87.5
Nursing home or rehabilitation facility (%)	0.2	0.6	0.2	0.7	0.9	1.6	0	0.5	0	0	0	0
Acute care hospital (%)	0.6	0.8	0.7	0.7	0	0.8	1.2	0.5	1.4	0	0	1.3
Living, no data (%)	3.3	2.1	2.9	2.0	2.5	0.8	3.0	1.6	2.7	1.7	3.3	5.0
Dead (%)	17.6	12.8	13.2	12.3	9.3	19.5	11.4	6.5	19.2	24.1	16.7	6.3
No. of patients	518	517	448	447	118	123	167	186	73	58	90	80
P value	0.02		0.60		0.04		0.06		0.67		0.14	
Median time since surgery (mo)	17.7		17.7		17.7		17.7		17.7		17.8	
27 Mo												
Private home (%)	73.8	72.8	79.1	74.9	81.1	61.2	79.0	83.1	75.9	61.9	78.9	85.5
Nursing home or rehabilitation facility (%)	0.3	0.8	0.3	0.6	1.1	1.0	0	0.7	0	0	0	0
Acute care hospital (%)	0.8	0.5	0.6	0.6	1.1	1.0	0	0.7	1.9	0	0	0
Living, no data (%)	4.2	4.0	4.4	3.7	4.4	4.1	7.3	3.4	1.9	0	1.4	6.5
Dead (%)	21.0	22.0	15.6	20.3	12.2	32.7	13.7	12.2	20.4	38.1	19.7	8.1
No. of patients	401	401	339	350	90	98	124	148	54	42	71	62
P value	0.74		0.16		0.002		0.41		0.11		0.25	
Median time since surgery (mo)	26.7		26.8		26.7		26.8		26.6		26.9	

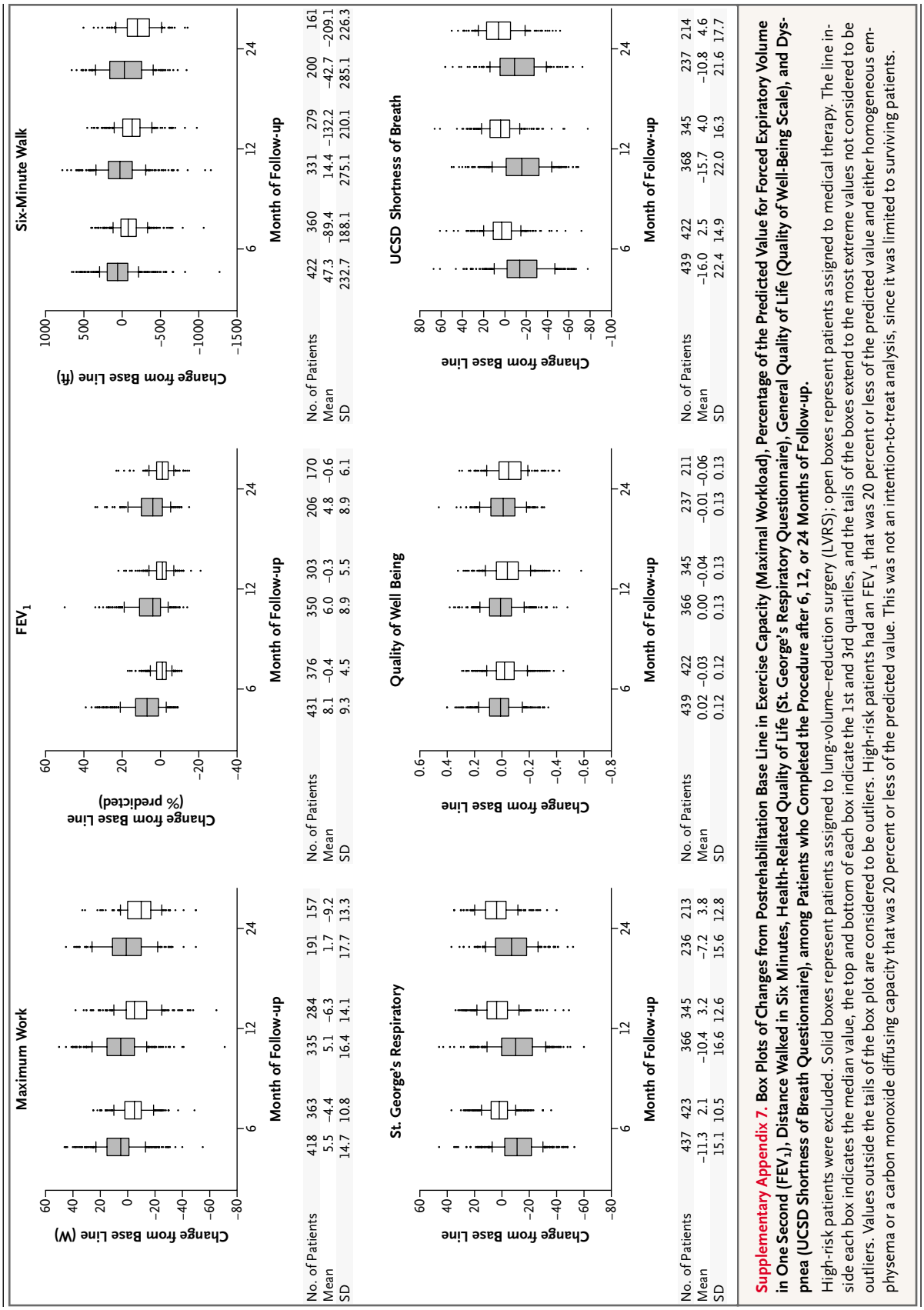
* High-risk patients had a forced expiratory volume in one second that was 20 percent or less of the predicted value and either homogeneous emphysema or a carbon monoxide diffusing capacity that was 20 percent or less of the predicted value. Upper-lobe predominance of emphysema was judged subjectively by each center's radiologist; choices were upper-lobe predominance, lower-lobe predominance, diffuse, or superior segments of lower lobes predominantly involved; the latter three choices were grouped as non–upper-lobe predominance. A low base-line exercise capacity was defined as a postrehabilitation base-line maximal workload at or below the sex-specific 40th percentile (25 W for women and 40 W for men); a high exercise capacity was defined as a workload above this threshold. All subgroup analyses excluded high-risk patients. P values are for homogeneity.



Supplementary Appendix 6. Histograms of Changes from Postrehabilitation Base Line in Distance Walked in Six Minutes, Health-Related Quality of Life (St. George's Respiratory Questionnaire), and Dyspnea (UCSD Shortness of Breath Questionnaire) after 6, 12, and 24 Months of Follow-up.

High-risk patients were excluded. The category "missing" includes patients who were too ill to complete the procedure or who declined to complete the procedure but did not explain why. P values were determined by the Wilcoxon rank-sum test. The degree to which the bars are shifted to the upper left of the chart indicates the degree of relative benefit of lung-volume–reduction surgery (LVRS) over medical treatment. The percentage shown in each quadrant is the percentage of patients in the specified treatment group with a change in the outcome falling into that quadrant. High-risk patients had an FEV_1 that was 20 percent or less of the predicted value and either homogeneous emphysema or a carbon monoxide diffusing capacity that was 20 percent or less of the predicted value. This was an intention-to-treat analysis.

Supplement to National Emphysema Treatment Trial Research Group. A Randomized Trial Comparing Lung-Volume–Reduction Surgery with Medical Therapy for Severe Emphysema. N Engl J Med 2003;348:2059-73.



	Maximum Work				FEV1				Six-Minute Walk			
No. of Patients	418	363	335	284	431	376	350	303	422	360	331	279
Mean	5.5	−4.4	5.1	−6.3	8.1	−0.4	6.0	−0.3	47.3	−89.4	14.4	−132.2
SD	14.7	10.8	16.4	14.1	9.3	4.5	8.9	5.5	232.7	188.1	275.1	210.1

No. of Patients	191	157	206	170	439	422	366	345	237	211	368	345
Mean	1.7	−9.2	4.8	−0.6	0.02	−0.03	0.00	−0.04	−0.01	−0.06	−15.7	4.0
SD	17.7	13.3	8.9	6.1	0.12	0.12	0.13	0.13	0.13	0.13	22.0	16.3

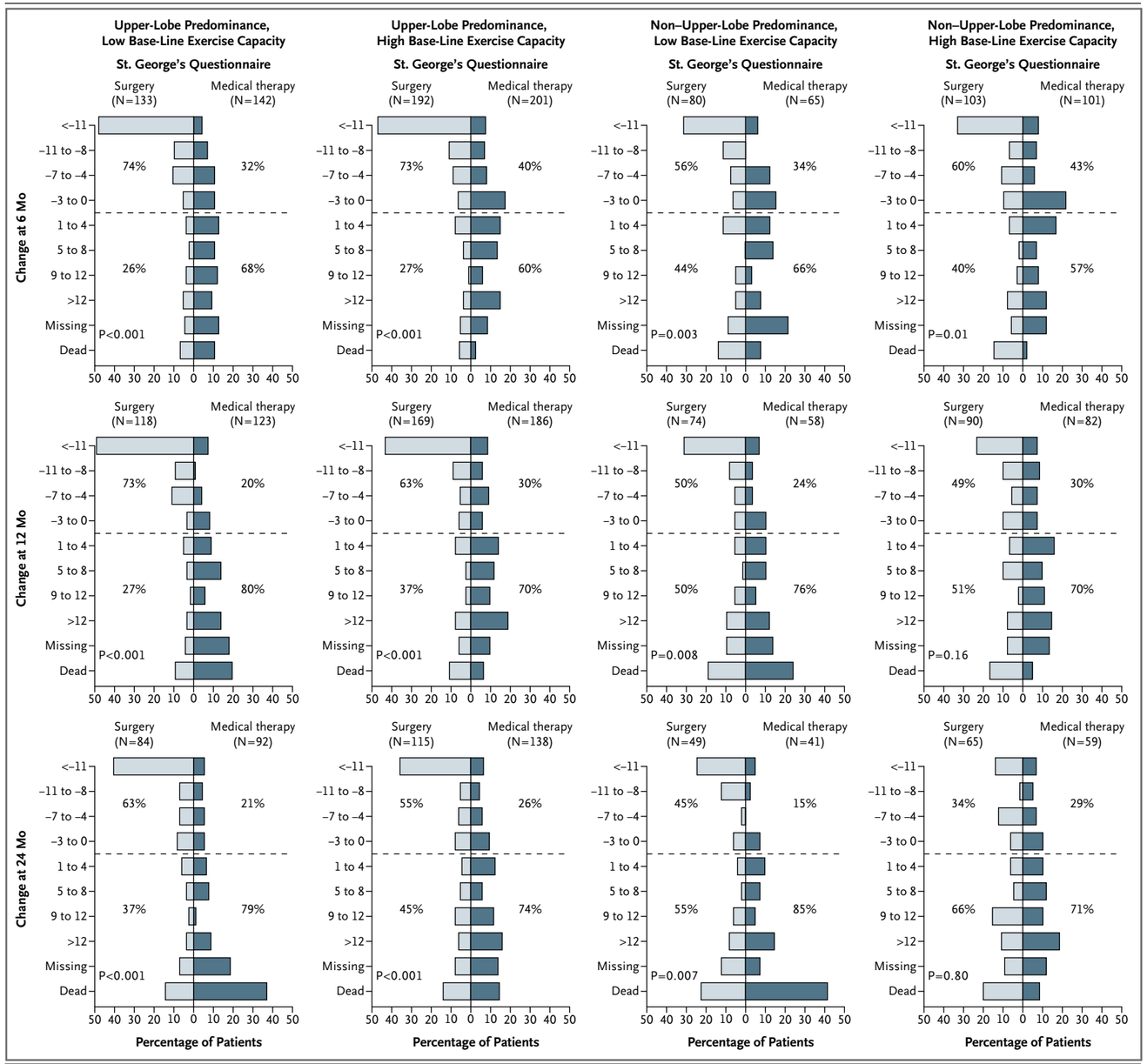
	St. George's Respiratory				Quality of Well Being				UCSD Shortness of Breath			
No. of Patients	437	423	366	345	439	422	366	345	237	211	368	345
Mean	−11.3	2.1	−10.4	3.2	0.02	−0.03	0.00	−0.04	−0.01	−0.06	−15.7	4.0
SD	15.1	10.5	16.6	12.6	0.12	0.12	0.13	0.13	0.13	0.13	22.0	16.3

No. of Patients	236	213	206	170	439	422	366	345	237	211	368	345
Mean	−7.2	3.8	4.8	−0.6	0.02	−0.03	0.00	−0.04	−0.01	−0.06	−15.7	4.0
SD	15.6	12.8	8.9	6.1	0.12	0.12	0.13	0.13	0.13	0.13	22.0	16.3

No. of Patients	236	213	206	170	439	422	366	345	237	211	368	345
Mean	−7.2	3.8	4.8	−0.6	0.02	−0.03	0.00	−0.04	−0.01	−0.06	−15.7	4.0
SD	15.6	12.8	8.9	6.1	0.12	0.12	0.13	0.13	0.13	0.13	22.0	16.3

Supplementary Appendix 7. Box Plots of Changes from Postrehabilitation Base Line in Exercise Capacity (Maximal Workload), Percentage of the Predicted Value for Forced Expiratory Volume in One Second (FEV_1), Distance Walked in Six Minutes, Health-Related Quality of Life (St. George's Respiratory Questionnaire), General Quality of Life (Quality of Well-Being Scale), and Dyspnea (UCSD Shortness of Breath Questionnaire), among Patients who Completed the Procedure after 6, 12, or 24 Months of Follow-up.

High-risk patients were excluded. Solid boxes represent patients assigned to lung-volume–reduction surgery (LVRS); open boxes represent patients assigned to medical therapy. The line inside each box indicates the median value, the top and bottom of each box indicate the 1st and 3rd quartiles, and the tails of the boxes extend to the most extreme values not considered to be outliers. Values outside the tails of the box plot are considered to be outliers. High-risk patients had an FEV_1 that was 20 percent or less of the predicted value and either homogeneous emphysema or a carbon monoxide diffusing capacity that was 20 percent or less of the predicted value. This was not an intention-to-treat analysis, since it was limited to surviving patients.



Supplementary Appendix 8. Histograms of Changes in Health-Related Quality of Life (St. George's Respiratory Questionnaire) after 6, 12, and 24 Months of Follow-up among Subgroups of Non–High-Risk Patients.

The category "missing" includes patients who were too ill to complete the procedure or who declined to complete the procedure but did not explain why. P values were determined by the Wilcoxon rank-sum test; the degree to which the bars are shifted to the upper left of the chart indicates the degree of relative benefit of lung-volume–reduction surgery (LVRS) over medical treatment. The percentage shown in each quadrant is the percentage of patients in the specified treatment group with a change in outcome falling into that quadrant. High-risk patients had a forced expiratory volume in one second that was 20 percent or less of the predicted value and either homogeneous emphysema or a carbon monoxide diffusing capacity that was 20 percent or less of the predicted value. Low base-line exercise capacity was defined as a maximal workload at or below the sex-specific 40th percentile (25 W for women, 40 W for men); high exercise capacity was defined as a workload above this threshold. This was an intention-to-treat analysis.

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Lung volume reduction surgery for diffuse emphysema (Review)

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Cochrane Database of Systematic Reviews 2016, Issue 10. Art. No.: CD001001.
DOI: 10.1002/14651858.CD001001.pub3.

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[Intervention Review]

Lung volume reduction surgery for diffuse emphysema

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ABSTRACT

Background

Lung volume reduction surgery (LVRS) performed to treat patients with severe diffuse emphysema was reintroduced in the nineties. Lung volume reduction surgery aims to resect damaged emphysematous lung tissue, thereby increasing elastic properties of the lung. This treatment is hypothesised to improve long-term daily functioning and quality of life, although it may be costly and may be associated with risks of morbidity and mortality. Ten years have passed since the last version of this review was prepared, prompting us to perform an update.

Objectives

The objective of this review was to gather all available evidence from randomised controlled trials comparing the effectiveness of lung volume reduction surgery (LVRS) versus non-surgical standard therapy in improving health outcomes for patients with severe diffuse emphysema. Secondary objectives included determining which subgroup of patients benefit from LVRS and for which patients LVRS is contraindicated, to establish the postoperative complications of LVRS and its morbidity and mortality, to determine which surgical approaches for LVRS are most effective and to calculate the cost-effectiveness of LVRS.

Search methods

We identified RCTs by using the Cochrane Airways Group Chronic Obstructive Pulmonary Disease (COPD) register, in addition to the online clinical trials registers. Searches are current to April 2016.

Selection criteria

We included RCTs that studied the safety and efficacy of LVRS in participants with diffuse emphysema. We excluded studies that investigated giant or bullous emphysema.

Data collection and analysis

Two independent review authors assessed trials for inclusion and extracted data. When possible, we combined data from more than one study in a meta-analysis using RevMan 5 software.

Main results

We identified two new studies (89 participants) in this updated review. A total of 11 studies (1760 participants) met the entry criteria of the review, one of which accounted for 68% of recruited participants. The quality of evidence ranged from low to moderate owing to an unclear risk of bias across many studies, lack of blinding and low participant numbers for some outcomes. Eight of the studies compared LVRS versus standard medical care, one compared two closure techniques (stapling vs laser ablation), one looked at the effect of buttressing the staple line on the effectiveness of LVRS and one compared traditional 'resectional' LVRS with a non-resectional surgical approach. Participants completed a mandatory course of pulmonary rehabilitation/physical training before the procedure commenced. Short-term

mortality was higher for LVRS (odds ratio (OR) 6.16, 95% confidence interval (CI) 3.22 to 11.79; 1489 participants; five studies; moderate-quality evidence) than for control, but long-term mortality favoured LVRS (OR 0.76, 95% CI 0.61 to 0.95; 1280 participants; two studies; moderate-quality evidence). Participants identified post hoc as being at high risk of death from surgery were those with particularly impaired lung function, poor diffusing capacity and/or homogenous emphysema. Participants with upper lobe-predominant emphysema and low baseline exercise capacity showed the most favourable outcomes related to mortality, as investigators reported no significant differences in early mortality between participants treated with LVRS and those in the control group (OR 0.87, 95% CI 0.23 to 3.29; 290 participants; one study), as well as significantly lower mortality at the end of follow-up for LVRS compared with control (OR 0.45, 95% CI 0.26 to 0.78; 290 participants; one study). Trials in this review furthermore provided evidence of low to moderate quality showing that improvements in lung function parameters other than forced expiratory volume in one second (FEV_1), quality of life and exercise capacity were more likely with LVRS than with usual follow-up. Adverse events were more common with LVRS than with control, specifically the occurrence of (persistent) air leaks, pulmonary morbidity (e.g. pneumonia) and cardiovascular morbidity. Although LVRS leads to an increase in quality-adjusted life-years (QALYs), the procedure is relatively costly overall.

Authors' conclusions

Lung volume reduction surgery, an effective treatment for selected patients with severe emphysema, may lead to better health status and lung function outcomes, specifically for patients who have upper lobe-predominant emphysema with low exercise capacity, but the procedure is associated with risks of early mortality and adverse events.

PLAIN LANGUAGE SUMMARY

Lung volume reduction surgery for adults with diffuse emphysema

Review question

Does lung volume reduction surgery improve lung function and quality of life, without leading to an increased chance of death, higher rates of illness after the procedure and higher costs for patients with severe emphysema, and which surgical methods lead to the best results in these patients?

Background

Emphysema causes severe damage to the lungs, which leads to breathing problems. Lung volume reduction surgery (LVRS) may help improve symptoms by removing the most diseased and non-functioning parts of the lung. However, this procedure has been the centre of much controversy with its possible benefit being outweighed by potential harms and costs.

Study characteristics

This review examined the research published up to the 14th of April, 2016, and identified 11 studies involving 1760 participants. Eight of the studies compared LVRS versus standard medical care, one compared two closure techniques (stapling vs laser ablation), one looked at the effect of buttressing the staple line on the effectiveness of LVRS and one compared a traditional approach to LVRS with a 'non-resectional' surgical approach. All participants completed a mandatory course of pulmonary rehabilitation/physical training before the procedure commenced.

Key results

This review found that people undergoing LVRS were at increased risk of death at three months after the procedure. By the end of follow-up, death rates were lower for participants treated with LVRS than for those given standard medical care. Participants who were characterised by poor lung function with a particular distribution of diseased tissue in their lungs were at higher risk of death at three months and throughout one large study. One study identified a group of participants who responded better to LVRS than other participants, making them especially suitable for this treatment. The benefit of surgery for surviving participants was significant in terms of quality of life, exercise capacity and lung function, but costs of the procedure are relatively high, and patients had a greater chance of adverse events after the procedure.

Quality of the evidence

The quality of the data reported is low to moderate in nature owing to some methodological issues of the trials (lack of blinding, unclear risk of bias). The results presented in this review are largely dominated by one influential study, which accounted for 68% of the participants.

Approved by the AUA Board of Directors
April 2018

Authors' disclosure of potential conflicts of interest and author/staff contributions appear at the end of the article.

ERECTILE DYSFUNCTION: AUA GUIDELINE

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The Panel would like to dedicate this Guideline to the memory of our friend and colleague, Ralph Alterowitz. We will forever be grateful to his contributions and devotion to the field of men's sexual health. He brought compassion and joy to all of those who were fortunate enough to work with him.

Executive Summary

The sexual response cycle is conceptualized as a sequential series of psychophysiological states that usually occur in an orderly progression. These phases were characterized by Masters and Johnson as desire, arousal, orgasm, and resolution. Erectile dysfunction (ED) can be conceptualized as an impairment in the arousal phase of sexual response and is defined as the consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual satisfaction, including satisfactory sexual performance.[1,2] The Panel believes that shared decision-making is the cornerstone of the treatment and management of ED, a model that relies on the concepts of autonomy and respect for persons in the clinical encounter. It is also a process in which the patient and the clinician together determine the best course of therapy based on a discussion of the risks, benefits and desired outcome. Using this approach, all men should be informed of all treatment options that are not medically contraindicated to determine the appropriate treatment. Although many men may choose to begin with the least invasive option, the Panel notes that it is valid for men to begin with any type of treatment, regardless of invasiveness or reversibility. Men also may choose to forego treatment. In each scenario, the clinician's role is to ensure that the man and his partner have a full understanding of the benefits and risks/burdens of the various management strategies.

Methodology

A systematic review of the literature using the Pubmed, Embase, and Cochrane databases (search dates 1/1/1965 to 7/29/17) was conducted to identify peer-reviewed publications relevant to the diagnosis and treatment of ED. The review yielded an evidence base of 999 articles after application of inclusion/exclusion criteria. These publications were used to create the guideline statements. If sufficient evidence existed, then the body of evidence for a particular treatment was assigned a strength rating of A (high quality evidence; high certainty), B (moderate quality evidence; moderate certainty), or C (low quality evidence; low certainty). Evidence-based statements of Strong, Moderate, or Conditional Recommendation, which can be supported by any body of evidence strength, were developed based on the balance of benefits and risks/burdens to men and their partners. Additional information is provided as Clinical Principles and Expert Opinion when insufficient evidence existed.

Section 11.0

New Discussion Items

PET Scan for Prostate Cancer

Plain Language Summary:

Coverage question: Should OHP cover a specific type of imaging test to see whether prostate cancer has spread to other parts of the body?

Should OHP cover this treatment? Yes, for people diagnosed with more severe forms of prostate cancer.

Note: This issue summary is identical to what appeared in the August 17, 2023 and September 28, 2023 meeting materials, except that an additional related code (C9156) for the necessary medication was added to the recommendation after the August meeting. This medication is necessary for PSMA PET scans.

Coverage Question: Should limited coverage of PET scan for evaluation of prostate cancer in certain clinical scenarios be added?

Question source: Dr. Steve Kornfeld, urology

Background: PET scans are used in many cancers to aid in diagnosis, staging, restaging and monitoring. PET scans are only covered for a limited subset of cancers based on Diagnostic Guideline D22. Dr. Kornfeld asked that currently lack of coverage for PET scans in prostate cancer be re-evaluated based on newer NCCN guidelines.

PSMA-PET refers to a growing body of radiopharmaceuticals that target prostate specific membrane antigen (PSMA) on the surface of prostate cells. Because of the high density of PSMA receptors on the surface of cancer cells relative to adjacent prostate, PSMA-PET has the advantage of high signal-to-noise relative to adjacent tissues.

Previous HSC/HERC reviews:

PET scans have been extensively reviewed over the past 20 years. The most recent changes were adding PET scan coverage for initial staging of breast cancer in 2018, and expanding this indication to monitoring treatment of metastatic breast cancer in 2021. PET scan coverage was added for use in management of active therapy of classic Hodgkin's lymphoma in 2021. Coverage for Alzheimer's disease for patients being considered for treatment with aducanumab or similar FDA approved medications for treatment of Alzheimer's disease was added in 2021.

The most recent PET scan review was conducted in November, 2022. Prostate cancer was not discussed as an indication during that review.

PET Scan for Prostate Cancer

Current Prioritized List/Coverage status:

Diagnostic Procedure File
• CPT 78815 Positron emission tomography (PET) with concurrently acquired computed tomography (CT) for attenuation correction and anatomical localization imaging; skull base to mid-thigh
• CPT 78816 Positron emission tomography (PET) with concurrently acquired computed tomography (CT) for attenuation correction and anatomical localization imaging; whole body

ICD-10-CM C61 (Malignant neoplasm of prostate) is on line 329 CANCER OF PROSTATE GLAND

DIAGNOSTIC GUIDELINE D22, PET SCANS
Diagnosis:
PET Scans are covered for diagnosis only when:

A) The PET scan is for evaluation of either:
   1) Solitary pulmonary nodules, small cell lung cancer and non-small cell lung cancer, OR
   2) Evaluation of cervical lymph node metastases when CT or MRI do not demonstrate an obvious primary tumor, AND

B) The PET scan will
   1) Avoid an invasive diagnostic procedure, OR
   2) Assist in determining the optimal anatomic location to perform an invasive diagnostic procedure.

Initial staging:
PET scans are covered for the initial staging when:

A) The staging is for one of the following cancers/situations:
   1) Cervical cancer only when initial MRI or CT is negative for extra-pelvic metastasis
   2) Head and neck cancer when initial MRI or CT is equivocal
   3) Colon cancer
   4) Esophageal cancer
   5) Solitary pulmonary nodule
   6) Non-small cell lung cancer
   7) Lymphoma
   8) Melanoma
   9) Breast cancer ONLY when metastatic disease is suspected AND standard imaging results are equivocal or suspicious
   10) Small cell lung cancer
   11) Neuroendocrine tumors
   12) Multiple myeloma
   13) Thyroid cancers; AND

B) Clinical management of the patient will differ depending on the stage of the cancer identified and either:
   1) the stage of the cancer remains in doubt after standard diagnostic work up, OR
   2) PET replaces one or more conventional imaging studies when they are insufficient for clinical management of the patient.

Monitoring:

PET Scan for Prostate Cancer

For monitoring tumor response during active therapy for purposes of treatment planning, PET is covered for

A) classic Hodgkin's lymphoma treatment

B) metastatic breast cancer ONLY when a change in therapy is contemplated AND PET scan was the imaging modality initially used to find the neoplasm being monitored.

Restaging:

Restaging is covered only when:

A) the cancer has staging covered above, AND

B) initial therapy has been completed, AND

C) the PET scan is conducted for

1) detecting residual disease, or
2) detecting suspected recurrence, or
3) determining the extent of a known recurrence.

Other indications:

PET scans are covered for preoperative evaluation of the brain in patients who have intractable seizures and are candidates for focal surgery. PET scans are covered for patients being considered for treatment with aducanumab or similar FDA approved medications for treatment of Alzheimer's disease.

Non-covered conditions/situations:

A) PET scans are NOT covered to monitor tumor response during the planned course of therapy for any cancer other than classic Hodgkin's lymphoma or the limited indication described above for metastatic breast cancer.

B) PET scans are NOT covered for routine follow up of cancer treatment or routine surveillance in asymptomatic patients.

C) PET scans are NOT covered for cardiac evaluation.

Evidence:

1) **Jadvar 2022**, appropriate use criteria for prostate-specific membrane antigen PET imaging
    a. Expert consensus
    b. Appropriate use of PSMA PET
        i. Newly diagnosed unfavorable intermediate-, high-risk, or very-high-risk prostate cancer [high level evidence]
        ii. Newly diagnosed unfavorable intermediate-, high-risk, or very-high-risk prostate cancer with negative/equivocal or oligometastatic disease on conventional imaging [supportive evidence]
        iii. PSA persistence or PSA rise from undetectable level after radical prostatectomy [high quality evidence]
        iv. PSA rise above nadir after definitive radiotherapy [high quality evidence]
        v. nmCRPC (M0) on conventional imaging
            1. There was some discussion by the panel regarding final scoring for this scenario, primarily because it was unclear how PSMA PET would change management, as all drugs approved in the M0 CRPC space are also

approved for the metastatic setting. Overall, there is an appreciation that external beam radiation is being used to treat patients with oligometastatic CRPC, with some preliminary data on its effectiveness; therefore, PSMA PET is important for correctly characterizing disease in these patients. On this basis, the panel decided to support PSMA PET as appropriate in this clinical scenario

Expert guidelines:

1) **NCCN 1.2023** Prostate Cancer
    a. Initial clinical assessment and staging evaluation
        i. For symptomatic patients and/or those with a life expectancy of greater than 5 years, bone and soft tissue imaging is appropriate for patients with unfavorable intermediate-risk, high-risk, and very-high-risk prostate cancer:
            1. Bone imaging can be achieved by conventional technetium-99m-MDP bone scan.
                a. Plain films, CT, MRI, or PET/CT or PET/MRI with F-18 sodium fluoride, C-11 choline, F-18 fluciclovine, Ga-68 prostate-specific membrane antigen (PSMA)-11, or F-18 piflufolastat PSMA can be considered for equivocal results on initial bone imaging.
            2. Soft tissue imaging of the pelvis, abdomen, and chest can include chest CT and abdominal/pelvic CT or abdominal/pelvic MRI. mpMRI is preferred over CT for pelvic staging.
            3. Alternatively, Ga-68 PSMA-11 or F-18 piflufolastat PSMA PET/CT or PET/MRI can be considered for bone and soft tissue (full body) imaging.
                a. Because of the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to conventional imaging (CT, MRI) at both initial staging and biochemical recurrence, the Panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA-PET/CT or PSMA-PET/MRI can serve as an equally effective, if not more effective front-line imaging tool for these patients.
    b. Work up for progression
        i. Castrate levels of testosterone should be documented if clinically indicated in patients with signs of progression, with adjustment of ADT as necessary. If serum testosterone levels are <50 ng/dL, the patient should undergo disease workup with bone and soft tissue imaging:
            1. Bone imaging can be achieved by conventional technetium-99m-MDP bone scan.
                a. Plain films, CT, MRI, or PET/CT or PET/MRI with F-18 sodium fluoride, C-11 choline, F-18 fluciclovine, Ga-68 PSMA-11, or F-18 PyL PSMA can be considered for equivocal results on initial bone imaging.
            2. Soft tissue imaging of pelvis, abdomen, and chest can include chest CT and abdominal/pelvic CT or abdominal/pelvic MRI.

3. Alternatively, Ga-68 PSMA-11 or F-18 PyL PSMA PET/CT or PET/MRI can be considered for bone and soft tissue (full body) imaging.
    a. Because of the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to conventional imaging (CT, MRI) at both initial staging and biochemical recurrence, the Panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA-PET/CT or PSMA-PET/MRI can serve as an equally effective, if not more effective frontline imaging tool for these patients.

c. The use of these PET tracers can lead to changes in clinical management. The FALCON trial showed that results of F-18 fluciclovine PET/CT in 104 patients with biochemical recurrence after definitive therapy resulted in a change in management for 64%. In addition, the LOCATE trial demonstrated that fluciclovine frequently changed management plans in patients with biochemical recurrence. In a similar fashion, data also show that PSMA PET has the ability to change radiation treatment planning in 53% (N = 45) of patients with high- and very-high-risk prostate cancer using PSMA-11 as well as change management in over half of a prospective cohort of 635 patients with BCR. However, whether changes to treatment planning because of PET tracers have an impact on long-term survival remains to be studied

2) **Lowrance 2023**, American Urological Association guideline for advanced prostate cancer
    a. Patients diagnosed with aggressive cancer defined by D'Amico risk factors (cT3a or greater, Grade Group 4/5, or PSA>20ng/mL) should undergo routine bone scan and cross-sectional imaging (CT or MRI) or PET imaging at the time of diagnosis. Utilization of PSMA PET may lead to the diagnosis of metastatic disease not previously detected with conventional imaging. While this detection of metastases at lower PSA levels is helpful in guiding therapy, it is important to note that the clinical trials for treatment did not use PET imaging; therefore, it is unknown if volume of disease on PET imaging can accurately classify patients into high- and low-risk groups
    b. In patients with PSA recurrence after failure of local therapy who are at higher risk for the development of metastases (e.g., PSADT <12 months), clinicians should perform periodic staging evaluations consisting of cross-sectional imaging (CT, MRI) and technetium bone scan, and/or preferably PSMA PET imaging. (Clinical Principle)
    c. Clinicians should utilize PSMA PET imaging preferentially, where available, in patients with PSA recurrence after failure of local therapy as an alternative to conventional imaging due to its greater sensitivity, or in the setting of negative conventional imaging. (Expert Opinion)
    d. Clinicians should assess non-metastatic CRPC patients for development of metastatic disease using conventional or PSMA PET imaging at intervals of 6 to 12 months. (Expert Opinion)
    e. In metastatic CRPC patients with disease progression (PSA or radiographic progression or new disease-related symptoms) having previously received docetaxel and androgen pathway inhibitor, who are considering 177Lu-PSMA-617, clinicians should order PSMA PET imaging. (Expert Opinion)
    f. Clinicians should offer 177Lu-PSMA-617 to patients with progressive metastatic CRPC having previously received docetaxel and androgen pathway inhibitor with a positive PSMA PET imaging study. (Strong Recommendation; Evidence Level Grade: B)
    g. Discussion

PET Scan for Prostate Cancer

i. The prostate cancer community has witnessed considerable developments in the detection of disease with next generation prostate cancer imaging. PET-CT has emerged as a sensitive and specific imaging test to detect prostate cancer metastases, particularly among men with biochemical recurrence after primary therapy.

Other payer policies:

1) Aetna 2023
    a. Aetna considers fluciclovine f-18 PET or choline c-11 PET medically necessary for restaging of men with a suspected recurrence of prostate cancer who meet *all* of the following criteria:
        i. Member has previously been treated with prostatectomy and/or radiation therapy; *and*
        ii. Member has a consecutive rise in PSA; *and*
        iii. PSA ≥ 1 ng/mL; *and*
        iv. CT scan and bone scan are negative for metastatic disease.
    b. Aetna considers Ga-68 PSMA-11 and piflufolastat F-18 (Pylarify) medically necessary for newly diagnosed and suspected recurrence of prostate cancer
2) Evicore/Cigna 2023
    a. PET scan is not covered for the initial work up or staging of prostate cancer
        i. PET/CT with any radiotracers are considered experimental/investigational for initial evaluation of prostate cancer
    b. PET scan is covered for restaging or recurrence of prostate cancer when a patient has all of the following:
        i. Prior treatment with prostatectomy and/or radiation therapy and
        ii. Consecutive rise in PSA and
        iii. PSA ≥1 ng/mL and
        iv. Recent CT scan and bone scan are negative for metastatic disease and
        v. Individual is a candidate for salvage local therapy

Expert input:

Jen-Jane Liu, OHSU urology

It [PSMA PET] definitely enhances detection of disease, and per NCCN guidelines is listed as a staging option with anyone with Gleason grade group 3 (4+3) and above and for biochemical recurrence after treatment of primary prostate cancer.

I think that the data for staging is strong in terms of enhanced sensitivity. It enhances detection, and this can potentially change management (change # of places you decide to radiate, opt out of surgery if widely metastatic disease). Whether that results in long term progression free or overall survival I do not think we know yet. For biochemical recurrence it can be useful to determine whether disease is localized and help direct therapy from that standpoint.

I use it frequently for staging now if insurance will approve, and most of the time for recurrence if PSA is high enough.

If I had to prioritize, I think coverage for biochemic recurrence is more important because this does affect choice of local therapy. For staging, it would be nice, but since we don't know if it enhances survival and there is conventional imaging available (bone scan, CT/MRI), it may not be as crucial in changing patient outcomes.

Chris Amling, OHSU urology

PSMA PET is currently covered for restaging (evaluation of recurrent disease after treatment), but often not approved for initial staging. As I understand it, this is in large part because it is FDA approved for the former but not the latter. The bottom line is that most of us who treat prostate cancer patients think that is should be covered for initial staging of higher risk prostate cancers (the ones listed), because it is more sensitive and specific in detecting metastatic disease (which could alter treatment approach), and because it could eliminate the need for pre-treatment bone scan and CT scan (current standard of care).

Steve Kornfeld, urologist

I can provide a summary based on NCCN. Note NCCN for prostate is quite old. I suspect when they update PSMA PET will be pushed even more. In general I feel that Oncologists over use PET. Especially to further stage known stage 4 and to follow metastatic disease on tx.

WE are not talking about standard PET, but PET directed toward PSMA. This is a specific Prostate Cancer only PET

Prostate has a number of unique features. Only in Prostate is a rising PSA after definitive local therapy considered a biochemical recurrence (vs rising tumor marker). M0 (biochemical recurrence) is treated differently than M1 (metastatic recurrence). Prostate is one of a very few cancers that has a radiopharmaceutical tx requiring specific PET imaging positivity.

PET Scan for Prostate Cancer

HERC staff summary:

PSMA PET imaging is listed by NCCN as an alternative imaging modality for the initial evaluation of intermediate and high risk prostate cancer. Expert imaging guidelines give PSMA PET imaging for newly diagnosed unfavorable intermediate-, high-risk, or very-high-risk prostate cancer a high level evidence. However, AUA guidelines note that PSMA PET as initial imaging for this group was not included in treatment studies and the impact on outcomes is not yet known. Additionally, the private payers surveyed generally did not cover PET for this indication. Local experts recommend covering for both staging and restaging.

NCCN also lists PSMA PET as one imaging option for recurrent disease. The AUA guidelines recommend PSMA PET imaging as the preferred imaging modality for recurrent disease. PET for recurrent disease is generally covered by private insurance and is the more highly recommended use of PET by local experts.

HERC staff recommends adding coverage of PSMA PET imaging for staging and restaging of prostate cancer in intermediate and high risk disease based on expert guidelines and expert input.

HERC staff recommendations:

1) Modify Diagnostic Guideline D22 as shown below
2) Advise HSD to add HCPCS C9156 (Flotufolastat f 18, diagnostic, 1 millicurie) to the Ancillary file for use in PSMA PET scanning

DIAGNOSTIC GUIDELINE D22, PET SCANS

Diagnosis:

PET Scans are covered for diagnosis only when:

A) The PET scan is for evaluation of either:
   1) Solitary pulmonary nodules, small cell lung cancer and non-small cell lung cancer, OR
   2) Evaluation of cervical lymph node metastases when CT or MRI do not demonstrate an obvious primary tumor, AND

B) The PET scan will
   1) Avoid an invasive diagnostic procedure, OR
   2) Assist in determining the optimal anatomic location to perform an invasive diagnostic procedure.

Initial staging:

PET scans are covered for the initial staging when:

A) The staging is for one of the following cancers/situations:
   1) Cervical cancer only when initial MRI or CT is negative for extra-pelvic metastasis
   2) Head and neck cancer when initial MRI or CT is equivocal
   3) Colon cancer
   4) Esophageal cancer
   5) Solitary pulmonary nodule
   6) Non-small cell lung cancer
   7) Lymphoma
   8) Melanoma

9) Breast cancer ONLY when metastatic disease is suspected AND standard imaging results are equivocal or suspicious
10) Small cell lung cancer
11) Neuroendocrine tumors
12) Multiple myeloma
13) Thyroid cancers
14) PSMA PET for unfavorable intermediate, high-risk, or very-high-risk prostate cancer

AND

B) Clinical management of the patient will differ depending on the stage of the cancer identified and either:
1) the stage of the cancer remains in doubt after standard diagnostic work up, OR
2) PET replaces one or more conventional imaging studies when they are insufficient for clinical management of the patient.

Monitoring:
For monitoring tumor response during active therapy for purposes of treatment planning, PET is covered for
A) classic Hodgkin's lymphoma treatment
B) metastatic breast cancer ONLY when a change in therapy is contemplated AND PET scan was the imaging modality
initially used to find the neoplasm being monitored.

Restaging:
Restaging is covered only when:
A) the cancer has staging covered above, AND
B) initial therapy has been completed, AND
C) the PET scan is conducted for
1) detecting residual disease, or
2) detecting suspected recurrence, or
3) determining the extent of a known recurrence

Other indications:
PET scans are covered for preoperative evaluation of the brain in patients who have intractable seizures and are candidates for focal surgery. PET scans are covered for patients being considered for treatment with aducanumab or similar FDA approved medications for treatment of Alzheimer's disease.

Non-covered conditions/situations:
A) PET scans are NOT covered to monitor tumor response during the planned course of therapy for any cancer other than classic Hodgkin's lymphoma or the limited indication described above for metastatic breast cancer.
B) PET scans are NOT covered for routine follow up of cancer treatment or routine surveillance in asymptomatic patients.
C) PET scans are NOT covered for cardiac evaluation.

Appropriate Use Criteria for Prostate-Specific Membrane Antigen PET Imaging

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Prostate cancer is the most common cancer diagnosis in men in the United States and a leading cause of cancer-related morbidity and mortality (*1*). It can exist along a wide spectrum of aggressiveness and severity, from indolent, very-low-risk, localized prostate cancer to life-threatening, very-high-risk, metastatic prostate cancer. For a newly diagnosed patient in a given clinical state, especially early in the disease, the spectrum of appropriate therapeutic options may range from no intervention to multimodality therapy. Accurate assessment of the extent of disease (e.g., metastatic vs. localized prostate cancer) is essential for guiding treatment decisions. Decision making for the clinical use of imaging and for the development of new imaging technology can both be organized by the framing principles outlined in Prostate Cancer Working group 3 (*2*).

Imaging plays a critical role in that assessment, which has traditionally been done in men at high risk for metastatic disease using a ^{99m}Tc-methylene diphosphate bone scan and CT (*3*). Significant advances toward developing more sensitive imaging techniques for detecting the extent of prostate cancer include PET radiopharmaceuticals. Although useful across a wide variety of cancer types, ^{18}F-FDG PET has had limited applicability in prostate cancer staging (*4*). Novel radiopharmaceuticals such as ^{18}F-fluciclovine and choline PET have been used increasingly in the biochemical recurrence (BCR) setting but have limited specificity (*5*,*6*).

INTRODUCTION

Prostate-Specific Membrane Antigen (PSMA) PET

The increasing use of radiopharmaceuticals that target the PSMA is based on growing scientific evidence that supports their favorable imaging performance. Many PSMA-targeted imaging agents are being evaluated, and 2 are currently approved by the U.S. Food and Drug Administration: ^{18}F-DCFPyL and ^{68}Ga-PSMA-11. Additional agents are being evaluated in phase III trials in the United States, including ^{18}F-PSMA-1007 (NCT04239742 and NCT04487847), ^{18}F-rhPSMA-7.3 (NCT04186819 and NCT04186845), ^{18}F-CTT1057 (NCT04838626), ^{68}Ga-PSMA-R2 (NCT03490032), and ^{64}Cu-SAR-bisPSMA (NCT04868604). Although there may be small differences between each radiopharmaceutical, there is no evidence to date that one specific radiopharmaceutical has improved diagnostic characteristics compared with another (*7*,*8*). For the purpose of this appropriate use criteria (AUC) document, we will treat all PSMA PET radiotracers as equivalent and refer to them as a class (e.g., PSMA PET).

Safety and Dosimetry of PSMA PET

Given the subpharmacologic mass dose and high specific activity administered, PSMA PET radiotracers, similar to other radiopharmaceuticals, have an excellent safety profile. For ^{68}Ga-PSMA-11, the proPSMA study showed no adverse events, and a safety evaluation from 2 prospective multicenter trials reported only minor changes in vital signs such as blood pressure and heart rate, with no medical interventions required (*9*). A similar safety profile has been observed with ^{18}F-DCFPyL, with no adverse events attributable to the radiotracer reported from the first-in-human trial (*10*).

The dosimetry for both ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL is comparable to that of other radiotracers in terms of whole-body exposure (Table 1). ^{68}Ga-PSMA-11 has a calculated effective dose of 0.017 mSv/MBq, equating to 4.4 mSv for a 259 MBq (7 mCi) injected dose, with the highest uptake organ being the kidney at 0.37 mGy/MBq (*11*). The total effective dose of ^{18}F-DCFPyL per mCi is similar to that of ^{68}Ga-PSMA-11 per mCi, coming in at 0.011 mSv/MBq, equating to 4.3 mGy for an injected dose of

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ADVANCED PROSTATE CANCER: AUA/SUO GUIDELINE

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SUMMARY

Purpose

The management of advanced prostate cancer is rapidly evolving. To assist in clinical decision-making, evidence-based guideline statements were developed to provide a rational basis for evidence-based treatment. This guideline covers advanced prostate cancer, including disease stages that range from prostate-specific antigen (PSA) recurrence after exhaustion of local treatment options to widespread metastatic disease.

Methodology

The systematic review utilized to inform this guideline was conducted by an independent methodological consultant. A research librarian conducted searches in Ovid MEDLINE (1998 to January Week 5 2019), Cochrane Central Register of Controlled Trials (through December 2018), and Cochrane Database of Systematic Reviews (2005 through February 6, 2019). An updated search was conducted prior to publication through January 20, 2020. In 2023, the Advanced Prostate Cancer guideline was updated through the AUA amendment process in which newly published literature is reviewed and integrated into previously published guidelines. The methodology team searched Ovid MEDLINE(R) ALL and the Cochrane Libraries for studies published between 2018 and March 16, 2022. Following initial report review, the Panel suggested additional abstracts that were assessed for inclusion as well.

GUIDELINE STATEMENTS

EARLY EVALUATION AND COUNSELING

1. In patients with suspicion of advanced prostate cancer and no prior histologic confirmation, clinicians should obtain tissue diagnosis from the primary tumor or site of metastases when clinically feasible. (*Clinical Principle*)

2. Clinicians should discuss treatment options with advanced prostate cancer patients based on life expectancy, comorbidities, preferences, and tumor characteristics. Patient care should incorporate a multidisciplinary approach when available. (*Clinical Principle*)

3. Clinicians should optimize pain control or other symptom support in advanced prostate cancer patients and encourage engagement with professional or community-based resources, including patient advocacy groups. (*Clinical Principle*)

BIOCHEMICAL RECURRENCE WITHOUT METASTATIC DISEASE AFTER EXHAUSTION OF LOCAL TREATMENT OPTIONS

Prognosis

4. Clinicians should inform patients with PSA recurrence after exhaustion of local therapy regarding the risk of developing metastatic disease and follow such patients with serial PSA measurements and clinical evaluation. Clinicians may consider radiographic assessments based on overall PSA and PSA kinetics. (*Clinical Principle*)

5. In patients with PSA recurrence after failure of local therapy who are at higher risk for the development of metastases (e.g., PSADT <12 months), clinicians should perform periodic staging evaluations consisting of cross-sectional imaging (CT, MRI) and technetium bone scan, and/or preferably PSMA PET imaging. (*Clinical Principle*)

6. Clinicians should utilize PSMA PET imaging preferentially, where available, in patients with PSA recurrence after failure of local therapy as an alternative to conventional imaging due to its greater sensitivity, or in the setting of negative conventional imaging. (*Expert Opinion*)

Treatment

7. For patients with a rising PSA after failure of local therapy and no demonstrated metastatic disease by imaging, clinicians should offer observation or clinical trial enrollment. (*Clinical Principle*)

8. ADT should not be routinely initiated in this population (*Expert Opinion*). However, if ADT is initiated in the absence of metastatic disease, intermittent ADT may be offered in lieu of continuous ADT. (*Conditional Recommendation; Evidence Level: Grade B*)

METASTATIC HORMONE-SENSITIVE PROSTATE CANCER

Prognosis

9. Clinicians should assess the extent of metastatic disease (lymph node, bone, and visceral metastases) in newly diagnosed mHSPC patients. (*Clinical Principle*)

10. In newly diagnosed mHSPC patients, clinicians should assess the extent of metastatic disease (low- versus high-volume). High-volume is defined as greater than or equal to four bone metastases with at least one metastasis outside of the spine/pelvis and/or the presence of visceral metastases. (*Moderate Recommendation: Evidence Level: Grade B*)

11. Clinicians should assess if a newly diagnosed mHSPC patient is experiencing symptoms from metastatic disease at the time of presentation to guide discussions of prognosis and further disease management. (*Moderate Recommendation; Evidence Level: Grade B*)

36. In patients with mismatch repair deficient or microsatellite instability-high (MSI-H) mCRPC, clinicians should offer pembrolizumab. (*Moderate Recommendation; Evidence Level: Grade C*)

BONE HEALTH

37. Clinicians should discuss the risk of osteoporosis associated with ADT and should assess the risk of fragility fracture in patients with advanced prostate cancer. (*Clinical Principle*)

38. Clinicians should recommend preventative treatment for fractures and skeletal-related events, including supplemental calcium, vitamin D, smoking cessation, and weight-bearing exercise, to advanced prostate cancer patients on ADT. (*Clinical Principle*)

39. In advanced prostate cancer patients at high fracture risk due to bone loss, clinicians should recommend preventative treatments with bisphosphonates or denosumab and referral to physicians who have familiarity with the management of osteoporosis when appropriate. (*Clinical Principle*)

40. Clinicians should prescribe a bone-protective agent (denosumab or zoledronic acid) for mCRPC patients with bony metastases to prevent skeletal-related events. (*Moderate Recommendation; Evidence Level: Grade B*)

Cardiac Resynchronization Therapy

Plain Language Summary:

Coverage question: Should OHP clarify the requirements for treatments that helps the heart beat with the right rhythm (pacemaker and heart defibrillator).

Should OHP make this change? Yes.

Coverage Question: Should cardiac resynchronization therapy indications on the Prioritized List be modified?

Question source: Tracy Muday, CCO medical director

Background: Cardiac resynchronization therapy (CRT) involves the insertion of an atrial and a ventricular pacemaker as well as a cardiac defibrillator. It is indicated in patients with heart failure and also left bundle branch block (LBBB) or prolonged QT interval.

There are a number of biventricular pacemakers designed to provide cardiac resynchronization therapy (CRT). Individuals meeting selection criteria for CRT therapy frequently are also considered candidates for an implantable cardioverter defibrillator (ICD). These persons may receive combined therapy with a combined CRT/ICD device. A biventricular pacemaker is designed to resynchronize the pumping action of the left ventricle. This type of pacing is called cardiac resynchronization therapy (CRT). Standard pacemakers pace the right side of the heart. In contrast, biventricular pacemakers pace both the right and left sides of the heart enabling the left ventricle to pump blood more efficiently. Biventricular pacemakers use three leads (one in the right atrium, and one in each ventricle) and have been investigated as a technique to coordinate the contraction of the ventricles, thus, improving the individual's hemodynamic status

Currently, cardiac resynchronization therapy is limited to patients requiring a bridge to transplant based on guideline note 95. Dr. Muday received a request for CRT for a patient who was not a transplant candidate and requested that the HERC reconsider current CRT coverage.

Previous HSC/HERC reviews:

The current wording regarding cardiac resynchronization was added to guideline note 95 in March 2018 as part of a review of implantable cardiac defibrillator (ICD) coverage. The wording was added based on what was then the CMS national coverage determination for ICDs. However, there was no specific discussion of cardiac resynchronization therapy in 2018, and it is unclear whether the added clause was mean to imply that CRT was ONLY covered for patients awaiting heart transplant or was ALSO covered for these patients.

Cardiac Resynchronization Therapy

Current Prioritized List/Coverage status:

CPT 33224 (Insertion of pacing electrode, cardiac venous system, for left ventricular pacing, with attachment to previously placed pacemaker or implantable defibrillator pulse generator (including revision of pocket, removal, insertion, and/or replacement of existing generator)) is on lines 69 ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION, 97 HEART FAILURE, 98 CARDIOMYOPATHY, 110 CONGENITAL HEART BLOCK; OTHER OBSTRUCTIVE ANOMALIES OF HEART, 189 CHRONIC ISCHEMIC HEART DISEASE, 281 LIFE-THREATENING CARDIAC ARRHYTHMIAS, 347 CARDIAC ARRHYTHMIAS

CPT 33225 (Insertion of pacing electrode, cardiac venous system, for left ventricular pacing, at time of insertion of implantable defibrillator or pacemaker pulse generator (eg, for upgrade to dual chamber system)) is on lines 69,97,98,110,189,281,347

CPT 33226 (Repositioning of previously implanted cardiac venous system (left ventricular) electrode (including removal, insertion and/or replacement of existing generator)) is on lines 69, 97, 98, 110, 189, 281, 285, 347

CPT 33230 (Insertion of implantable defibrillator pulse generator only; with existing dual leads) is on lines 97,98,110,281,285

CPT 33249 (Insertion or replacement of permanent implantable defibrillator system, with transvenous lead(s), single or dual chamber) is on lines 97,98,110,281,285

GUIDELINE NOTE 95, IMPLANTABLE CARDIAC DEFIBRILLATORS

Lines 97,98,110,281,285

Implantable cardiac defibrillators are included on these lines for patients with one or more of the following:

A) Patients with a personal history of sustained ventricular tachyarrhythmia or cardiac arrest due to ventricular fibrillation. Patients must have demonstrated one of the following:
   1) Documented episode of cardiac arrest due to ventricular fibrillation (VF), not due to a transient or reversible cause
   2) Documented sustained ventricular tachyarrhythmia (VT), either spontaneous or induced by an electrophysiology (EP) study, not associated with an acute myocardial infarction

B) Patients with a prior myocardial infarction and a measured left ventricular ejection fraction (LVEF) ≤ 0.30. Patients must not have:
   1) New York Heart Association (NYHC) classification IV heart failure; or
   2) Cardiogenic shock or symptomatic hypotension while in a stable baseline rhythm; or
   3) Had a coronary artery bypass graft (CABG) or percutaneous transluminal coronary intervention (PCI) with angioplasty and/or stenting, within past 3 months; or
   4) Had a myocardial infarction in the past 40 days; or
   5) Clinical symptoms or findings that would make them a candidate for coronary revascularization

C) Patients who have severe ischemic dilated cardiomyopathy but no personal history of sustained ventricular tachyarrhythmia or cardiac arrest due to ventricular fibrillation, and have New York Heart Association (NYHA) Class II or III heart failure, left ventricular ejection fraction (LVEF) ≤ 35%. Additionally, patients must not have:

1) Had a coronary artery bypass graft (CABG), or percutaneous coronary intervention (PCI) with angioplasty and/or stenting, within the past 3 months; or
2) Had a myocardial infarction within the past 40 days; or
3) Clinical symptoms and findings that would make them a candidate for coronary revascularization.

D) Patients who have severe non-ischemic dilated cardiomyopathy but no personal history of sustained ventricular tachyarrhythmia or cardiac arrest due to ventricular fibrillation, and have New York Heart Association (NYHA) Class II or III heart failure, left ventricular ejection fraction (LVEF) ≤ 35%, been on optimal medical therapy (OMT) for at least 3 months. Additionally, patients must not have:
   1) Had a coronary artery bypass graft (CABG), or percutaneous coronary intervention (PCI) with angioplasty and/or stenting, within the past 3 months; or
   2) Had a myocardial infarction within the past 40 days; or
   3) Clinical symptoms and findings that would make them a candidate for coronary revascularization.

E) Patients with documented familial, or genetic disorders with a high risk of life-threatening tachyarrhytmias (sustained ventricular tachycardia or ventricular fibrillation), to include, but not limited to, long QT syndrome or hypertrophic cardiomyopathy.

F) Patients with an existing ICD may receive an ICD replacement if it is required due to the end of battery life, elective replacement indicator (ERI) or device/lead malfunction.

For these patients identified in A-E, a formal shared decision making encounter must occur between the patient and a physician or qualified non-physician practitioner using an evidence-based decision tool on ICDs prior to initial ICD implantation. The shared decision making encounter may occur at a separate visit.

All indications above in A-F must meet the following criteria:

A) Patients must be clinically stable (e.g., not in shock, from any etiology);

B) Left ventricular ejection fraction (LVEF) must be measured by echocardiography, radionuclide (nuclear medicine) imaging, or catheter angiography;

C) Patients must not have:
   1) Significant, irreversible brain damage; or
   2) Any disease, other than cardiac disease (e.g., cancer, renal failure, liver failure) associated with a likelihood of survival less than 1 year; or
   3) Supraventricular tachycardia such as atrial fibrillation with a poorly controlled ventricular rate.

Exceptions to waiting periods for patients that have had a coronary artery bypass graft (CABG), or percutaneous coronary intervention (PCI) with angioplasty and/or stenting, within the past 3 months, or had a myocardial infarction within the past 40 days:

A) Cardiac Pacemakers: Patients who meet all CMS coverage requirements for cardiac pacemakers and who meet the criteria in this national coverage determination for an ICD may receive the combined device in one procedure at the time the pacemaker is clinically indicated;

B) Replacement of ICDs: Patients with an existing ICD may receive a ICD replacement if it is required due to the end of battery life, elective replacement indicator (ERI) or device/lead malfunction.

Cardiac Resynchronization Therapy

Other Indications:
For patients who are candidates for heart transplantation on the United Network for Organ Sharing (UNOS) transplant list awaiting a donor heart, coverage of ICDs, as with cardiac resynchronization therapy, as a bridge to transplant to prolong survival until a donor becomes available.

Expert guidelines:

1) **Heidenreich 2022**, AHA/ACC/HRSA guideline for the management of heart failure
   a) Recommends cardiac resynchronization therapy for patients with NYHA II-III or ambulatory IV, LVEF ≤ 35%, LBBB and QRS ≥ 150ms
      i) Class I (strong) recommendation
   b) Recommends cardiac resynchronization therapy for patients with NYHA II-III or ambulatory IV, LVEF ≤ 35%, QRS ≥ 150ms without LBBB
      i) Classa 2a (moderate) recommendation
   c) Recommends cardiac resynchronization therapy for patients with NYHA II-III or ambulatory IV, LVEF ≤ 35%, LBBB and QRS ≥ 120-149 msec
      i) Classa 2a (moderate) recommendation
   d) Recommends cardiac resynchronization therapy for patients with NYHA II-III or ambulatory IV, LVEF ≤ 35%, QRS ≥ 120-149 msec without LBBB
      i) Classa 2b (weak) recommendation
   e) Most of the relevant data for the guidelines of CRT in HF come from seminal trials published from 2002 to 2010. The first of these was the MIRACLE (Multicenter InSync Randomized Clinical Evaluation) trial, which took patients with LVEF ≤35%, moderate to severe HF, and QRS duration ≥130 ms.16 There was a benefit in the 6-minute walk test, QOL, functional HF classification, and LVEF. The COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure) trial, which enrolled NYHA class III to IV patients with QRS ≥120 ms, included 3 arms: GDMT, CRT-D, and CRT pacemaker (CRT-P).17 The primary end-point of death or hospitalization was decreased with CRT-P and CRT-D. The CARE-HF (Cardiac Resynchronization Heart Failure) trial included a similar group with NYHA class III to IV, LVEF ≤35%, QRS >120 ms, and showed a significant reduction in primary and endpoint of death or hospitalization.18 In the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial, patients with NYHA class I to II and LVEF ≤40% were randomized to CRT-D on for 1 year and CRT-D off for 1 year or vice versa.19 A HF composite endpoint was less common when CRT was activated. MADIT-CRT enrolled NYHA class I and II HF with LVEF ≤30% and QRS ≥130 ms and compared CRT-D with ICD.20 The primary endpoint of death or HF was reduced by CRT-D. The RAFT (Resynchronization-Defibrillation for Ambulatory Heart Failure) trial randomized patients with NYHA class II to III HF, LVEF ≤30%, QRS >120 ms, or paced QRS ≥200 ms and compared CRT-D with ICD.2 Again, there was a reduction in the primary endpoint of death or HF hospitalization.
   f) Extension of benefit to patients with narrow QRS has been attempted but has generally failed. In the RETHINQ (Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS) trial, patients with QRS duration < 130 ms were randomized to CRT or not. There was no benefit from CRT, but subgroup analysis showed there was a benefit with QRS durations between 120 and 130 ms. In the ECHO-CRT (Echocardiography Guided Cardiac Resynchronization Therapy) trial, patients with NYHA class III to IV HF,

LVEF ≤35% and a QRS duration ≤130 ms, and mechanical dysynchrony on echocardiography underwent randomization to CRT. There was no benefit to CRT in this trial. And in the LESSER-EARTH (Evaluation of Resynchronization Therapy for Heart Failure) trial, patients with severe LV dysfunction and QRS < 120 ms derived no benefit from CRT.51 The NARROW-CRT (Narrow QRS Ischemic Patients Treated With Cardiac Resynchronization Therapy) was the only trial that showed a benefit in a clinical composite score in patients with an indication for an ICD and QRS < 120 ms.

g) Subgroup analysis of the CRT trials has shown no benefit for those with LVEF ≤35%, non-LBBB 120 to 149, and NYHA class I-II HF

Other payer policies:

2) CMS LCD Cardiac resynchronization therapy
   a) CRT will be considered medically necessary when the following criteria for a given beneficiary are met:
      i) LVEF ≤ 35%, with ischemic or non-ischemic cardiomyopathy, on maximally tolerated guideline-directed medical therapy (GDMT) for at least 3 months and with no reversible causes; *and*
         (a) QRS ≥ 150 ms; and
         (b) Any type bundle branch block with evidence of dyssynchrony; and
         (c) NYHA class III or ambulatory IV HF
      ii) LVEF ≤ 35%, on maximally tolerated GDMT for at least 3 months and with no reversible causes; *and*
         (a) QRS ≥ 150 ms; and
         (b) LBBB; and
         (c) NYHA classes II, III or ambulatory IV HF
      iii) LVEF ≤ 35%, on maximally tolerated GDMT for at least 3 months and with no reversible causes; *and*
         (a) QRS 130-149 ms; and
         (b) LBBB; and
         (c) NYHA class II, III or ambulatory IV HF
      iv) In patients with atrial fibrillation (AF) or in sinus rhythm who have an indication for pacemaker implant for second or third degree atrioventricular (AV) block (including those who have or will have AV nodal ablation), or very prolonged first degree block with PR > 300 ms, *and*:
         (a) with an EF < 50%; and
         (b) with NYHA I, II or III class; and
         (c) anticipated frequent ventricular pacing
      v) Patients who are being paced from the RV frequently (generally considered at least > 40% of the time) and who develop worsening HF symptoms (NYHA class II-IV) with a decline in LVEF to a value < 40% may be considered for upgrade to CRT.*
         (a) *For an upgrade from standard pacing to CRT, this A/B Medicare Administrative Contractor (MAC) would expect documentation narrative regarding the risk-benefit balance for that individual patient and his/her degree of HF, QRS duration/morphology, etc. A “stand-alone” upgrade in patients with an existing pacemaker or implanted cardiac defibrillator should be considered carefully and based on the individual patient’s unique circumstances. Upgrades to CRT from

conventional RV pacing at the time of a needed generator change will be covered per the usual criteria as noted in all preceding coverage bullets.

b) Patients who meet all CMS coverage requirements for cardiac pacemakers, and who meet the criteria in the NCD for Implantable Automatic Defibrillators (20.4), may receive the combined devices in 1 procedure, at the time the biventricular pacemaker is clinically indicated.

c) Patients with an existing CRT device may receive a generator replacement if it is required due to the end of battery life, elective replacement indicator (ERI), or device/lead malfunction.

d) **Limitations:**

i) Noncovered Services: (CRT is unlikely to offer benefit and is probably associated with harm)

(a) Patients with a QRS < 130 ms (Exception to this non-coverage criterion would be in the case of patients undergoing AV nodal ablation or in need of RV pacing (due to second- or third-degree block or very long first degree block) that is expected to occur a majority of the time.)

(b) Patients with an EF $\geq$ 50%

(c) CRT in patients with non-ambulatory NYHA IV HF symptoms or on chronic inotropic HF therapy or with LV assist devices in place

3) Anthem BCBS 2022

a) Biventricular pacemakers for cardiac resynchronization therapy (CRT) are considered **medically necessary** for individuals who meet **all** of the following criteria:

i) NYHA functional Class II, III, or ambulatory Class IV symptoms* secondary to heart failure who remain symptomatic despite recommended, Guideline-directed medical therapy (GDMT) (which may include use of medications from the following drug classes, either individually or in combination for at least 3 months, unless contraindicated: renin-angiotensin system inhibition with angiotensin receptor-neprilysin inhibitors, angiotensin-converting enzyme inhibitors, or angiotensin [II] receptor blockers; beta blockers; mineralocorticoid receptor antagonists; and sodium-glucose cotransporter-2 inhibitors, when appropriate); **and**

ii) Have either:

(i) Left bundle branch block (LBBB) morphology and QRS duration of 120 to 149 ms; **or**

(ii) Any QRS morphology and QRS duration greater than or equal to 150 ms; **and**

(b) Left ventricular ejection fraction (LVEF) less than or equal to 35%; **and**

iii) In either:

(a) Sinus rhythm; **or**

(b) Atrial fibrillation when AV nodal ablation or pharmacologic rate control will allow near 100% ventricular pacing.

Expert input:

Dr. Eric Stecker from OHSU cardiology assisted HERC staff in drafting the guideline wording change recommendations

Cardiac Resynchronization Therapy

HERC staff summary:

The current wording in GN95 is unclear about intent of coverage for cardiac resynchronization therapy. CRT has never been explicitly discussed by HERC. The current guideline wording should be modified to clarify when CRT is a covered service.

HERC staff recommendation:

1) Modify GN95 as shown below
    a. Based on current ACC/AHA recommendations and expert input
    b. Additional edits are recommended by staff to clean up certain section

GUIDELINE NOTE 95, IMPLANTABLE CARDIAC DEFIBRILLATORS

Lines 97,98,110,281,285

Implantable cardiac defibrillators are included on these lines for patients with one or more of the following:

A) Patients with a personal history of sustained ventricular tachyarrhythmia or cardiac arrest due to ventricular fibrillation. Patients must have demonstrated one of the following:
    1) Documented episode of cardiac arrest due to ventricular fibrillation (VF), not due to a transient or reversible cause
    2) Documented sustained ventricular tachyarrhythmia (VT), either spontaneous or induced by an electrophysiology (EP) study, not associated with an acute myocardial infarction

B) Patients with a prior myocardial infarction and a measured left ventricular ejection fraction (LVEF) ≤ 0.30. Patients must not have:
    1) New York Heart Association (NYHC) classification IV heart failure; or
    2) Cardiogenic shock or symptomatic hypotension while in a stable baseline rhythm; or
    3) Had a coronary artery bypass graft (CABG) or percutaneous transluminal coronary intervention (PCI) with angioplasty and/or stenting, within past 3 months; or
    4) Had a myocardial infarction in the past 40 days; or
    5) Clinical symptoms or findings that would make them a candidate for coronary revascularization

C) Patients who have severe ischemic dilated cardiomyopathy but no personal history of sustained ventricular tachyarrhythmia or cardiac arrest due to ventricular fibrillation, and have New York Heart Association (NYHA) Class II or III heart failure, left ventricular ejection fraction (LVEF) ≤ 35%. Additionally, patients must not have:
    1) Had a coronary artery bypass graft (CABG), or percutaneous coronary intervention (PCI) with angioplasty and/or stenting, within the past 3 months; or
    2) Had a myocardial infarction within the past 40 days; or
    3) Clinical symptoms and findings that would make them a candidate for coronary revascularization.

D) Patients who have severe non-ischemic dilated cardiomyopathy but no personal history of sustained ventricular tachyarrhythmia or cardiac arrest due to ventricular fibrillation, and have New York Heart Association (NYHA) Class II or III heart failure, left ventricular ejection fraction (LVEF) ≤ 35%, been on optimal medical therapy (OMT) for at least 3 months. Additionally, patients must not have:

1) Had a coronary artery bypass graft (CABG), or percutaneous coronary intervention (PCI) with angioplasty and/or stenting, within the past 3 months; or
2) Had a myocardial infarction within the past 40 days; or
3) Clinical symptoms and findings that would make them a candidate for coronary revascularization.

E) Patients with documented familial, or genetic disorders with a high risk of life-threatening tachyarrhytmias (sustained ventricular tachycardia or ventricular fibrillation), to include, but not limited to, long QT syndrome or hypertrophic cardiomyopathy.

F) Patients with an existing ICD may receive an ICD replacement if it is required due to the end of battery life, elective replacement indicator (ERI) or device/lead malfunction.

For these patients identified in A-E, a formal shared decision making encounter must occur between the patient and a physician or qualified non-physician practitioner using an evidence-based decision tool on ICDs prior to initial ICD implantation. The shared decision making encounter may occur at a separate visit.

All indications above in A-F must meet the following criteria:

A) Patients must be clinically stable (e.g., not in shock, from any etiology);

B) Left ventricular ejection fraction (LVEF) must be measured by echocardiography, radionuclide (nuclear medicine) imaging, or catheter angiography;

C) Patients must not have significant contraindications~~:~~

~~1) Significant, irreversible brain damage; or~~

~~2) Any disease, other than cardiac disease (e.g., cancer, renal failure, liver failure) associated with a likelihood of survival less than 1 year; or~~

~~3) Supraventricular tachycardia such as atrial fibrillation with a poorly controlled ventricular rate.~~

Exceptions to waiting periods for patients that have had a coronary artery bypass graft (CABG), or percutaneous coronary intervention (PCI) with angioplasty and/or stenting, within the past 3 months, or had a myocardial infarction within the past 40 days:

A) Cardiac Pacemakers: Patients who meet all CMS coverage requirements for cardiac pacemakers and who meet the criteria in this guideline ~~national coverage determination~~ for an ICD may receive the combined device in one procedure at the time the pacemaker is clinically indicated;

B) Replacement of ICDs: Patients with an existing ICD may receive a ICD replacement if it is required due to the end of battery life, elective replacement indicator (ERI) or device/lead malfunction.

Other Indications:
For patients who are candidates for heart transplantation on the United Network for Organ Sharing (UNOS) transplant list awaiting a donor heart, ~~coverage of~~ ICDs~~, as with cardiac resynchronization therapy,~~ are only included on these lines ~~as~~ as a bridge to transplant to prolong survival until a donor becomes available.

Cardiac resynchronization therapy (CRT) ICD is only covered for patients with NYHA Class II-III and ambulatory IV heart failure with an ejection fraction ≤ 35% as well as one of the following:

1) left bundle branch block (LBBB) and a QRS complex over 120 msec; OR
2) QRS complex ≥ 150ms

CRT-pacemaker is covered for the following:

Cardiac Resynchronization Therapy

1) patients for whom CRT-ICD is covered
2) patients for whom CRT-ICD is excluded only due to high risk of competing mortality, or NYHA Class I heart failure, or hospitalized NYHA Class IV heart failure, or EF 35-40%

Circulation

AHA/ACC/HFSA CLINICAL PRACTICE GUIDELINE

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

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AIM: The "2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure" replaces the "2013 ACCF/AHA Guideline for the Management of Heart Failure" and the "2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure." The 2022 guideline is intended to provide patient-centric recommendations for clinicians to prevent, diagnose, and manage patients with heart failure.

METHODS: A comprehensive literature search was conducted from May 2020 to December 2020, encompassing studies, reviews, and other evidence conducted on human subjects that were published in English from MEDLINE (PubMed), EMBASE, the Cochrane Collaboration, the Agency for Healthcare Research and Quality, and other relevant databases. Additional relevant clinical trials and research studies, published through September 2021, were also considered. This guideline was harmonized with other American Heart Association/American College of Cardiology guidelines published through December 2021.

STRUCTURE: Heart failure remains a leading cause of morbidity and mortality globally. The 2022 heart failure guideline provides recommendations based on contemporary evidence for the treatment of these patients. The recommendations present an evidence-based approach to managing patients with heart failure, with the intent to improve quality of care and align with patients' interests. Many recommendations from the earlier heart failure guidelines have been updated with new evidence, and new recommendations have been created when supported by published data. Value statements are provided for certain treatments with high-quality published economic analyses.

*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry may apply; see Appendix 1 for detailed information. †ACC/AHA Representative. ‡ACC/AHA Joint Committee on Clinical Practice Guidelines Liaison. §ACC/AHA Task Force on Performance Measures Representative. ‖HFSA Representative.

ACC/AHA Joint Committee on Clinical Practice Guidelines Members, see page e986.

The American Heart Association requests that this document be cited as follows: Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, Fang JC, Fedson SE, Fonarow GC, Hayek SS, Hernandez AF, Khazanie P, Kittleson MM, Lee CS, Link MS, Milano CA, Nnacheta LC, Sandhu AT, Stevenson LW, Vardeny O, Vest AR, Yancy CW. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2022;145:e895–e1032. doi: 10.1161/CIR.0000000000001063

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Nasal Fracture Coverage Clarification

Plain Language Summary:

Coverage question: Should OHP cover treatments for a broken nose?

Should OHP cover this treatment? Yes, fixing a broken nose may need adjusting by hand, with or without using splints. This should be done within 14 days after the break happened. Rhinoplasty (a nose surgery) is needed when the nose is blocked and causing breathing problems.

Coverage Question: When should treatment of nasal fractures be included on a covered line and when on an uncovered line?

Question source: Holly Jo Hodges, CCO medical director

Background: The diagnosis codes and the treatment codes for nasal fracture appear on two lines, line 228 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES and line 557 DEVIATED NASAL SEPTUM, ACQUIRED DEFORMITY OF NOSE, OTHER DISEASES OF UPPER RESPIRATORY TRACT. There is no guideline or other indication regarding when nasal fractures are on the covered line and when on the uncovered.

There are guidelines regarding nasal surgery, but the lines for acute nasal fractures are not included in these guidelines. The coverage for treatment of acute nasal fractures needs to be clarified.

Previous HSC/HERC reviews:

Rhinoplasty was discussed in 2006 as part of cleft palate repair. Coverage was eventually added to the cleft palate line. In a larger discussion regarding repair of nose deformities at that time, the minutes state "The group did not want coverage for nasal deformities with only social impacts. The deformity must have significant physical impacts." A guideline was adopted in 2006 that read "GUIDELINE NOTE XXX RECONSTRUCTION OF THE NOSE Line 273 ICD-9 code 748.1 (Other anomalies of the nose) is on Line 273 only for reconstruction of absence of the nose and other severe nasal anomalies which significantly impair physical or social functioning." At a later discussion in 2010, it was reiterated that the HOSC members only wanted to cover repair of a nasal fracture that resulted functional problems rather than cosmesis.

Repairing nasal issues was again discussed in 2015. The reconstruction of the nose guideline was deleted. In 2016, fracture of the nasal bones that were closed and healing normally were moved from the covered upper line to the uncovered lower line as a consent item.

Nasal Fracture Coverage Clarification

Current Prioritized List/Coverage status:

ICD-10-CM Code	Code Description	Current Placement
S02.2XXA	Fracture of nasal bones, initial encounter for closed fracture	577 DEVIATED NASAL SEPTUM, ACQUIRED DEFORMITY OF NOSE, OTHER DISEASES OF UPPER RESPIRATORY TRACT
S02.2XXB	Fracture of nasal bones, initial encounter for open fracture	228 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES
S02.2XXD	Fracture of nasal bones, subsequent encounter for fracture with routine healing	577
S02.2XXG	Fracture of nasal bones, subsequent encounter for fracture with delayed healing	577
S02.2XXK	Fracture of nasal bones, subsequent encounter for fracture with nonunion	443 MALUNION AND NONUNION OF FRACTURE
CPT Code	**Code Description**	**Current Placement**
21315	Closed treatment of nasal bone fracture with manipulation; without stabilization	228
21320	Closed treatment of nasal bone fracture with manipulation; with stabilization	228
21325	Open treatment of nasal fracture; uncomplicated	228,577
21330	Open treatment of nasal fracture; complicated, with internal and/or external skeletal fixation	228,577
21335	Open treatment of nasal fracture; with concomitant open treatment of fractured septum	228,577
21336	Open treatment of nasal septal fracture, with or without stabilization	228
21337	Closed treatment of nasal septal fracture, with or without stabilization	228
30400	Rhinoplasty, primary; lateral and alar cartilages and/or elevation of nasal tip	466 CHRONIC SINUSITIS 506 NASAL POLYPS, OTHER DISORDERS OF NASAL CAVITY AND SINUSES 577
30410	Rhinoplasty, primary; complete, external parts including bony pyramid, lateral and alar cartilages, and/or elevation of nasal tip	466,506,577
30420	Rhinoplasty, primary; including major septal repair	228,466,506,577
30450	Rhinoplasty, secondary; major revision (nasal tip work and osteotomies)	228,466,506

Nasal Fracture Coverage Clarification

GUIDELINE NOTE 118, SEPTOPLASTY

Lines 42,119,246,287,466,506,525,577

Septoplasty is included on these lines when

A) The septoplasty is done to address symptomatic septal deviation or deformity which
   1) Fails to respond to a minimum 6 week trial of conservative management (e.g. nasal corticosteroids, decongestants, antibiotics); AND
   2) Results in one or more of the following:
      a. Persistent or recurrent epistaxis, OR
      b. Documented recurrent sinusitis felt to be due to a deviated septum and the patient meets criteria for sinus surgery in Guideline Note 35, SINUS SURGERY; OR
      c. Nasal obstruction with documented absence of other causes of obstruction likely to be responsible for the symptoms (for example, nasal polyps, tumor, etc.) [note: this indication is included only on Line 577; OR

B) Septoplasty is performed in association with cleft lip or cleft palate repair or repair of other congenital craniofacial anomalies; OR

C) Septoplasty is performed as part of a surgery for a neoplasm or facial trauma involving the nose.

Septoplasty is not covered for obstructive sleep apnea.

GUIDELINE NOTE 216, RHINOPLASTY

Lines 42,119,202,246,287,466,506,525

Rhinoplasty is included on these lines when

A) It is performed to correct a nasal deformity secondary to congenital cleft lip and/or palate or other severe congenital craniofacial anomaly; OR

B) It is performed as part of reconstruction after accidental or surgical trauma or disease (e.g., Wegener's granulomatosis, choanal atresia, nasal malignancy, abscess, septal infection with saddle deformity, or congenital deformity) AND
   1) There is prolonged, persistent obstructed nasal breathing unresponsive to a six week trial of conservative management (e.g. nasal corticosteroids, decongestants, antibiotics); AND
   2) Airway obstruction will not respond to septoplasty and turbinectomy alone; AND
   3) Photographs demonstrate an external nasal deformity; AND
   4) There is significant obstruction of one or both nares, documented by nasal endoscopy, computed tomography (CT) scan or other appropriate imaging modality; OR

C) There is nasal airway obstruction causing chronic rhinosinusitis when all of the following are met:
   1) The criteria for sinus surgery are met in Guideline Note 35, SINUS SURGERY; AND
   2) Airway obstruction will not respond to septoplasty and turbinectomy alone; AND
   3) Photographs demonstrate an external nasal deformity; AND
   4) There is significant obstruction of one or both nares), documented by nasal endoscopy, computed tomography (CT) scan or other appropriate imaging modality

Nasal Fracture Coverage Clarification

Line 42 CLEFT PALATE WITH AIRWAY OBSTRUCTION
Line 119 CHOANAL ATRESIA
202 SLEEP APNEA, NARCOLEPSY AND REM BEHAVIORAL DISORDER
246 LIFE-THREATENING EPISTAXIS
287 CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX
466 CHRONIC SINUSITIS
506 NASAL POLYPS, OTHER DISORDERS OF NASAL CAVITY AND SINUSES
525 BENIGN NEOPLASM OF NASAL CAVITIES, MIDDLE EAR AND ACCESSORY SINUSES

Expert guidelines:

1) **American Academy of Otolaryngology-Head and Neck Surgery 2021**, clinical indicators: nasal fracture
    a. Nasal fractures are common. If no airway obstruction or nasal deformity has occurred due to the fracture, surgical treatment may not be needed. For nasal fractures resulting in deformity or airway obstruction, surgery may be indicated to open the nasal passage and/or improve appearance. Surgery for nasal trauma may not be able to completely correct the traumatic deformity and/or may not correct preexisting deformities. Nasal infection, bleeding, or hematoma are possible, yet infrequent complications.

Nasal Fracture Coverage Clarification

HERC staff summary:

Acute nasal fracture should be on a covered line for either ED or primary care evaluation and initial treatment. Acute treatment may require manual realignment with or without internal or external splinting, which should be done within 14 days from when the fracture occurred. Rhinoplasty is only required when there is nasal blockage causing airway obstruction and is generally not done with acute nasal fractures.

All acute nasal fracture diagnosis codes should be moved to the covered line. All procedure codes for acute treatment should also be on the covered line. The rhinoplasty guideline should be modified to clarify that acute nasal fracture treatment is included on line 228, but treatment more than 14 days after the injury falls on line 577 unless criteria for nasal obstruction are met.

Other changes need to be made to GN 216. This guideline is attached to line 246 LIFE-THREATENING EPISTAXIS, which only has septoplasty CPT codes. Line 246 should only be attached to the septoplasty guideline.

HERC staff recommendations:

1) Add the following ICD-10-CM codes to line 228 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES and remove from line 577 DEVIATED NASAL SEPTUM, ACQUIRED DEFORMITY OF NOSE, OTHER DISEASES OF UPPER RESPIRATORY TRACT
    a. S02.2XXA Fracture of nasal bones, initial encounter for closed fracture
    b. S02.2XXD Fracture of nasal bones, subsequent encounter for fracture with routine healing
    c. S02.2XXG Fracture of nasal bones, subsequent encounter for fracture with delayed healing
2) Add the following ICD-10-CM codes to line 228 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES and remove from line 443 MALUNION AND NONUNION OF FRACTURE
    a. S02.2XXK Fracture of nasal bones, subsequent encounter for fracture with nonunion
3) Remove the following CPT codes from line 577 DEVIATED NASAL SEPTUM, ACQUIRED DEFORMITY OF NOSE, OTHER DISEASES OF UPPER RESPIRATORY TRACT
    a. 21325 Open treatment of nasal fracture; uncomplicated
    b. 21330 Open treatment of nasal fracture; complicated, with internal and/or external skeletal fixation
    c. 21335 Open treatment of nasal fracture; with concomitant open treatment of fractured septum
4) Remove the following CPT codes from line 228 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES
    a. 30420 Rhinoplasty, primary; including major septal repair
    b. 30450 Rhinoplasty, secondary; major revision (nasal tip work and osteotomies)
5) Modify GN118 as shown below
    a. Add line 202 SLEEP APNEA, NARCOLEPSY AND REM BEHAVIORAL DISORDER
6) Modify GN216 as shown below
    a. Remove line 202 SLEEP APNEA, NARCOLEPSY AND REM BEHAVIORAL DISORDER and line 246 LIFE-THREATENING EPISTAXIS from this guideline as it does not apply to diagnoses on these lines
    b. Add line 577 to the guideline

Nasal Fracture Coverage Clarification

c. Clarify which lines various sections refer to

GUIDELINE NOTE 118, SEPTOPLASTY

Lines 42,119,202,246,287,312,466,506,525,577

Septoplasty is included on line 312 for gender affirming treatment.

Septoplasty is included on lines 42, 119, 202, 246, 287,466, 506, 525 and 577 when

A) The septoplasty is done to address symptomatic septal deviation or deformity which
   1) Fails to respond to a minimum 6 week trial of conservative management (e.g. nasal corticosteroids, decongestants, antibiotics); AND
   2) Results in one or more of the following:
      a. Persistent or recurrent epistaxis, OR
      b. Documented recurrent sinusitis felt to be due to a deviated septum and the patient meets criteria for sinus surgery in Guideline Note 35, SINUS SURGERY; OR
      c. Nasal obstruction with documented absence of other causes of obstruction likely to be responsible for the symptoms (for example, nasal polyps, tumor, etc.) [note: this indication is included only on Line 577; OR

B) Septoplasty is performed in association with cleft lip or cleft palate repair or repair of other congenital craniofacial anomalies; OR

C) Septoplasty is performed as part of a surgery for a neoplasm or facial trauma involving the nose.

Septoplasty is not covered for obstructive sleep apnea.

GUIDELINE NOTE 216, RHINOPLASTY

Lines 42,119,~~202~~,~~246,~~287,312,466,506,525,577

Rhinoplasty is included on line 312 for gender affirming treatment.

Rhinoplasty is included on lines ~~42, 119, 202, 246, 287, 466, 506 and 525~~ 42 and 119, when A) it is performed to correct a nasal deformity secondary to congenital cleft lip and/or palate or other severe congenital craniofacial anomaly. ~~; OR~~

B) Rhinoplasty is included on lines 228, 287, 506, 525 and 577 when It is performed as part of reconstruction after accidental or surgical trauma or disease (~~e.g.,~~ for example Wegener's granulomatosis, ~~choanal atresia,~~ nasal malignancy, abscess, septal infection with saddle deformity~~, or congenital deformity~~) AND

1) There is prolonged, persistent obstructed nasal breathing unresponsive to a six week trial of conservative management (e.g. nasal corticosteroids, decongestants, antibiotics); AND
2) Airway obstruction will not respond to septoplasty and turbinectomy alone; AND
3) Photographs demonstrate an external nasal deformity; AND
4) There is significant obstruction of one or both nares, documented by nasal endoscopy, computed tomography (CT) scan or other appropriate imaging modality. ~~; OR~~

C) Rhinoplasty is included on line 466 when t~~T~~here is nasal airway obstruction causing chronic rhinosinusitis when all of the following are met:

1) The criteria for sinus surgery are met in Guideline Note 35, SINUS SURGERY; AND

Nasal Fracture Coverage Clarification

2) Airway obstruction will not respond to septoplasty and turbinectomy alone; AND
3) Photographs demonstrate an external nasal deformity; AND
4) There is significant obstruction of one or both nares), documented by nasal endoscopy, computed tomography (CT) scan or other appropriate imaging modality

Treatment of Liver Metastases

Plain Language Summary:

Coverage question: Liver metastases are tumors that started out in some other part of the body and have spread to the liver. Should OHP cover treatments for this condition?

Should OHP cover these treatments? Yes, certain types of treatments should be covered in limited cases.

Coverage Question: What treatments should be covered for cancer that is metastatic to the liver?

Question source: Kristin Garrett, CCO medical director

Background: Many cancers can metastasize to the liver, but the most common liver metastases is colorectal cancer. There are many treatments for cancer that has metastasized to the liver, including chemotherapy, surgical resection, radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation, and electro-coagulation.

Currently, Guideline Note 78 HEPATIC METASTASES limits treatment of liver metastases to hepatectomy/resection of the liver (CPT codes 47120, 47122,47125 or 47130). The CPT codes for other treatments, such as RFA, are on line 315 CANCER OF LIVER, but appear to be reserved for primary hepatocellular carcinoma. Guideline Note 78 was written in 2009, and the field of oncology has made vast strides in treatment of liver metastases since that time.

Dr. Garrett is requesting clarification of what treatments are actually intended to be paired with liver metastases (specifically colorectal cancer metastases).

In addition to Dr. Garrett's question, staff have reviewed the various treatments for liver metastases, and cryoablation of liver tumors (CPT 47383) was last reviewed in 2014 and placed on line 662/GN173 and should be re-reviewed as it has been almost 10 years since the last review.

Dr. Max Kaiser, CCO medical director and HERC member, has asked HERC staff to look at use of Yttrium-90 (Y-90) for treatment of metastatic disease to the liver for indications other than hepatocellular carcinoma (HCC) or colorectal cancer (CRC) metastatic to the liver. Since the last review of Y-90, the CPT code for this treatment has had a major description change. In 2019, CPT 79445 was specific for HCC or CRC metastatic to the liver. Currently, CPT 79445 is "Radiopharmaceutical therapy, by intra-arterial particulate administration."

Previous HSC/HERC reviews:
April 2006

Treatment of Liver Metastases

Discussion

Treatment of Liver Cancer: Little explained that the Commission previously considered embolization for tumor destruction using yttrium and elected not to place it on the list; however, the code for embolization remains. A case at OMAP resulted in her questioning whether appropriate treatments were listed on this line. [Kevin] Olson explained the different treatments, as follows: Radiofrequency ablation is insertion of an ultrasound catheter with use of heat to kill tissue, cryotherapy is the same thing except using a liquid nitrogen probe, chemoembolization is when a catheter is inserted into an artery that feeds the tumor, chemotherapy is infused then the artery is embolized with gel foam. The yttrium procedure does not involve embolization. All of these are used to treat both primary liver cancer and metastatic colon cancer. Saha asked if any of these treatments were controversial except the yttrium. Olson stated that for colon cancer metastatic only to the liver, resection can result in 25% long-term survival. Hepatic artery infusion with 5-FU improved outcomes as well. The data on RFA and cryotherapy is weaker. Chemoembolization results in shrinkage of tumor, but causes severe side-effects. RFA and yttrium have fewer side effects. Hepatic artery infusion is also effective, but systemic chemotherapy has improved to the point that it is rarely done anymore. Saha clarified that the task today is to determine if any of these treatments should be removed from the List. Olson stated that there are some cases where an isolated metastasis is too close to the bile duct to operate, and in those cases it makes sense to use RFA or cryo. He also said that yttrium treatment costs approximately $70,000

Actions: Do not delete any of the following codes from Line 489:
36260 - Insertion of implantable intra-arterial infusion pump
36262 - Removal of implanted intra-arterial infusion pump
37204 - Transcatheter occlusion or embolization
47370 - Laparoscopy, surgical, ablation of one or more liver tumors, RFA
47371 - Laparoscopy, surgical, ablation of one or more liver tumors, cryosurgical
47380 - Ablation, open, one or more liver tumors; RFA
47381 - Ablation, open, one or more liver tumors; cryosurgical 47382 - Ablation, percutaneous, one or more liver tumors; RFA Do not delete CPT code
36261, Revision of implanted intra-arterial infusion pump

Delete 79445 - Radoipharmaceutical therapy, by intra-arterial particulate administration, from Line 489.

June 2009

Discussion

Hepatic metastases Livingston introduced the summary document on liver metastases. The recommendation was to move 197.7 (Secondary malignant neoplasm of the liver) from Line 613 SECONDARY AND ILL-DEFINED MALIGNANT NEOPLASMS to Line 338 CANCER OF LIVER, to pair with 47120-47130 (Hepatectomy, resection of liver), with a coding specification to avoid inappropriate pairings: “Hepatic metastases (ICD-9 code 197.7) are covered in this line only when paired with CPT code 47120-47130 and only when no other extrahepatic metastases are present.” Saha asked whether this diagnosis could have the cancer care statement of intent criteria applied to it. Livingston reported that the 5 year survival is not reported. Historically, survival is 3-25 month survival without treatment and 14-17 months with treatment. Mckelvey asked whether survival was affected by type of primary cancer; Livingston replied that all studies

reviewed were on colorectal cancer. Saha noted that based on the 5 year survival data, it appears that treatment of solitary liver metastases meets the criteria in the SOI of improvement of 30%. Historically, best survival 2 yrs, this data shows 3 years, which is 50% increase in survival. The suggestion was made that solitary liver metastases be moved to the colon cancer line, as this was where the evidence for treatment was strongest. Smits noted that CPT treatment codes would also need to be added to this line. Coffman cautioned that moving CPT codes would allow them to pair with other types of cancer as the ICD-9 code for liver metastases is generic/not specific for metastatic colorectal cancer. Saha asked whether the HSC could make a guideline restricting use of this code for metastatic colon/rectal cancer if this diagnosis was added to the liver cancer line; the answer from HSC staff was yes. Suggested wording for a guideline was: "Hepatic metastases (ICD-9 code 197.7) are covered in this line only for 1) a covered primary cancer treatment of which meets our statement of intent for cancer treatment, 2) when paired with CPT code 47120-47130 and 3) when no other extrahepatic metastases are present." Gubler disagreed, that thought that the solitary liver metastases diagnosis should be left under the liver cancer line, with treatment left to clinical judgment. Saha noted that in this situation, rare cases of other diagnoses could be treated under the exceptions process. Shaffer stated that DMAP don't grant exceptions when the HSC has a clear guideline stating limitations to coverage. Kirk objected as well, noting that the hearings/exceptions process for such exceptions are a strain to the plans. A patient with a terminal cancer below the line who has a hepatic met above the line will get an argument that the lower diagnoses (the terminal cancer) should be covered to help benefit the covered diagnosis (the liver metastases), as counterintuitive as that may be. Saha noted that some cases may involve an unknown primary cancer. He noted that in this case, there is no evidence that you would prolong life by treating the solitary metastasis. The decision was to consider placing on either the colorectal or the liver cancer line, with a guideline to be developed by HSC staff and sent to Saha for comment. This topic will be revisited at the December meeting.

Action: HSC staff to develop a guideline restricting treatment of solitary hepatic metastases to evidence based situations, and to determine whether placement should be on the colorectal or liver cancer lines. Staff will forward this guideline/ recommendation to Saha and return to the December meeting for further discussion

December 2009

Solitary liver metastases Livingston introduced a summary regarding solitary liver metastases. There was minimal discussion.

Action
Move 197.7 (Secondary malignant neoplasm of the liver) from Line 612 to Line 338. Guideline adopted as shown in Appendix A. [This guideline later became Guideline Note 78]

GUIDELINE NOTE XXX, HEPATIC METASTASES
Line 338
Hepatic metastases (ICD-9 code 197.7) are covered in this line only when:
1) Treatment of the primary tumor is covered on a funded line in accordance with the criteria in guideline note XX Treatment of Cancer With Little or No Benefit Provided Near the End of Life;
2) There are no other extrahepatic metastases; and,

3) The only treatment covered is hepatectomy/resection of liver (CPT codes 47120, 47122, 47125 or 47130)

November 2014

Cryoablation of liver tumors (CPT 47383)

1) Cryoablation of liver tumors is a minimally invasive treatment of either primary hepatocellular carcinoma or metastatic disease to the liver
2) Radiofrequency ablation of liver tumors (CPT 47382) is covered on the liver cancer line
3) Evidence
    a. **NICE 2010,** guidance for treatment of liver metastases
        i. Current evidence on the safety of cryotherapy for the treatment of liver metastases appears adequate in the context of treating patients whose condition has such a poor prognosis, but the evidence on efficacy is inadequate in quality. Therefore cryotherapy for the treatment of liver metastases should only be used with special arrangements for clinical governance, consent and audit or research.
    b. **Bala 2013**, Cochrane review of cryotherapy for liver metastases
        i. 1 RCT, with high risk of bias
            1. 123 patients, randomized to cryotherapy or conventional surgery
            2. The patients were followed for up to 10 years (minimum five months). Mortality at the last follow-up was 81% (51/63) in the cryotherapy group and 92% (55/60) in the conventional surgery group (RR 0.88; 95% CI 0.77 to 1.02); that is, no statistically significant difference was observed.
            3. Recurrence in the liver was observed in 86% (54/63) of the patients in the cryotherapy group and 95% (57/60) of the patients in the conventional surgery group (relative risk (RR) 0.9; 95% CI 0.8 to 1.01); that is, no statistically significant difference was observed.
        ii. **Authors' conclusions** On the basis of one randomised clinical trial with high risk of bias, there is insufficient evidence to conclude if in patients with liver metastases from various primary sites cryotherapy brings any significant benefit in terms of survival or recurrence compared with conventional surgery. In addition, there is no evidence for the effectiveness of cryotherapy when compared with no intervention. At present, cryotherapy cannot be recommended outside randomised clinical trials.
    c. **Awad 2009**, Cochrane review of cryotherapy for hepatocellular carcinoma
        i. No trials identified
        ii. **Authors' conclusions** At present, there is no evidence to recommend or refute cryotherapy for patients with hepatocellular carcinoma. Randomised clinical trials with low-risk of bias may help in defining the role of cryotherapy in the treatment of hepatocellular carcinoma.
4) HERC staff recommendation: **Non-covered List**
    a. Experimental for both hepatocellular carcinoma and metastatic disease

November 2019

Treatment of Liver Metastases

Yttrium 90 therapy was discussed in 11/2019. High level evidence for the use of Yttrium 90 (RCT level evidence) exists only for use of Y90 as first line treatment for HCC. Y-90 treatment was limited to HCC only in GN185. The codes for Y-90 were added to the liver cancer line. Since 2019, the code descriptions have changed. In 2019, CPT 79445 was specific for HCC or CRC metastatic to the liver. Currently, CPT 79445 is "Radiopharmaceutical therapy, by intra-arterial particulate administration."

Current Prioritized List/Coverage status:

Line 157 CANCER OF COLON, RECTUM, SMALL INTESTINE AND ANUS
Contains no liver lesion treatment CPT codes

Diagnosis included on line 315 CANCER OF LIVER:
ICD-10-CM C22.9 Malignant neoplasm of liver, not specified as primary or secondary
ICD-10-CM C78.7 Secondary malignant neoplasm of liver and intrahepatic bile duct

Treatments included on line 315 CANCER OF LIVER:

CPT 36260-36262: placement, revision and removal of implantable intra-arterial infusion pump (eg, for chemotherapy of liver)
CPT 37243 Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction
CPT 47120-47130: Hepatectomy, resection of liver
CPT 47370 Laparoscopy, surgical, ablation of 1 or more liver tumor(s); radiofrequency
CPT 47371 Laparoscopy, surgical, ablation of 1 or more liver tumor(s); cryosurgical
CPT 47380 Ablation, open, of 1 or more liver tumor(s); radiofrequency
CPT 47381 Ablation, open, of 1 or more liver tumor(s); cryosurgical
CPT 47382 Ablation, 1 or more liver tumor(s), percutaneous, radiofrequency

GUIDELINE NOTE 78, HEPATIC METASTASES

Line 315

ICD-10-CM C78.7 Hepatic metastases are included on this line only when:

A) Treatment of the primary tumor is covered on a funded line in accordance with the criteria in Guideline Note 12 PATIENT-CENTERED CARE OF ADVANCED CANCER;
B) There are no other extrahepatic metastases; and,
C) The only treatment covered is hepatectomy/resection of liver (CPT codes 47120, 47122,47125 or 47130).

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

Line 662

The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Treatment of Liver Metastases

Procedure Code	Intervention Description	Rationale	Last Review
47383	Ablation, 1 or more liver tumor(s), percutaneous, cryoablation No evidence of effectiveness for both hepatocellular carcinoma and metastatic disease	No evidence of effectiveness for both hepatocellular carcinoma and metastatic disease	November, 2014

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:

A) Downsizing tumors in patients who could become eligible for curative treatment (transplant, ablation, or resection), OR

B) Palliative treatment of incurable patients with unresectable or inoperable tumors that are not amenable to ablation therapy and

1) who have good liver function (Child-Pugh class A or B) and
2) good performance status (ECOG performance status 0-2), and
3) who have intermediate stage disease with tumors > 5 cm OR advanced stage HCC with unilateral (not main) portal vein tumor thrombus

Pretreatment mapping is included on this line, however, pre-treatment embolization is not included on this line due to insufficient evidence of effectiveness.

Treatment of Liver Metastases

Evidence:

Ablation vs liver resection

1) **NICE 2020**, treatment for metastatic colorectal cancer in the liver amenable to treatment with curative intent
    a. Evidence on ablation vs resection
        i. Very low quality evidence from 1 retrospective cohort study (N=138) showed no clinically important difference in overall survival between people who received RFA alone and those who underwent resection alone for metastatic colorectal cancer in the liver.
        ii. Quality of life
            1. No evidence was identified to inform this outcome.

Cryotherapy

1) **Bala 2019**, Cochrane review of cryotherapy for liver metastases
    a. Included only RCTs in their search strategy
    b. We found no randomized clinical trials comparing cryotherapy versus no intervention or versus systemic treatments
    c. We identified one randomized clinical trial comparing cryotherapy with conventional surgery. The trial included 123 participants with solitary, or multiple unilobar or bilobar liver metastases; 63 participants received cryotherapy and 60 received conventional surgery. The primary sites for the metastases were colon and rectum (66.6%), stomach (7.3%), breast (6.5%), skin (4.9%), ovaries (4.1%), uterus (3.3%), kidney (3.3%), intestines (1.6%), pancreas (1.6%), and unknown (0.8%). The trial was not reported sufficiently enough to assess the risk of bias of the randomization process, allocation concealment, or presence of blinding. It was also not possible to assess incomplete outcome data and selective outcome reporting bias. The certainty of evidence was low because of risk of bias and imprecision. The participants were followed for up to 10 years (minimum five months). The trial reported that the mortality at 10 years was 81% (51/63) in the cryotherapy group and 92% (55/60) in the conventional surgery group. The calculated by us relative risk (RR) with 95% Confidence Interval (CI) was: RR 0.88, 95% CI 0.77 to 1.02. We judged the evidence as low-certainty evidence.
    d. Regarding adverse events and complications, separately and in total, our calculation showed no evidence of a difference in recurrence of the malignancy in the liver: 86% (54/63) of the participants in the cryotherapy group and 95% (57/60) of the participants in the conventional surgery group developed a new malignancy (RR 0.90, 95% CI 0.80 to 1.01; low-certainty evidence). The frequency of reported complications was similar between the cryotherapy group and the conventional surgery group, except for postoperative pain. Both insignificant and pronounced pain were reported to be more common in the cryotherapy group while intense pain was reported to be more common in the conventional surgery group. There were no intervention-related mortality or bile leakages. We identified no evidence for health-related quality of life, cancer mortality, or time to progression of liver metastases.
    e. Authors' conclusions: The evidence for the effectiveness of cryotherapy versus conventional surgery in people with liver metastases is of low certainty. We are uncertain about our estimate and cannot determine whether cryotherapy compared with conventional surgery is beneficial or harmful. We found no evidence for the benefits or harms of cryotherapy compared with no intervention, or versus systemic treatments

Treatment of Liver Metastases

2) **Khanmohammadi 2023**, systematic review and meta-analysis of percutaneous cryoablation for liver metastases
    a. N=15 articles (692 patients)
        i. 9 retrospective cohort studies, 6 prospective cohort studies
        ii. Any type of metastatic cancer, colon cancer being the most common diagnosis
    b. Mean overall survival ranged from 14.5–29 months. The rate of local recurrence in the included studies ranged from 9.4% to 78%, and local control progression-free survival ranged from 1 to 31 months. One-year disease-free survival rate ranged from 58.3 to 63.6%, and the mean disease-free survival was between 3.67 and 7.74 months. One-, two-, and three-year overall survival rates were 56.3–92.3%, 31.3–71.9%, and 18.8–41% among the studies, and the mean overall survival ranged from 14.5–29 months
    c. The total QoL decreased one week after the cryoablation procedure (-3.08 [95% Confidence interval: -4.65, -1.50], p-value 7.39], p-value <0.01) and three months (3.75 [2.25, 5.24], p-value <0.01) after the procedure
    d. Increased liver enzymes (144), pain (140), fever (134), thrombocytopenia (59), pleural effusion (31), malaise (6), self-limited liver bleeding (2), grade1/2 complications (2), freezing sensation (1) pneumothorax (1), and biliary leak (1) were among the post-procedure complications
    e. Conclusion: Cryoablation is an effective procedure for the treatment of liver metastases, especially in cases that are poor candidates for liver resection. It could significantly improve QoL with favorable local recurrence.

Expert guidelines:

Colorectal cancer

1) **NCCN 2.2023** Colon cancer
    a. Resection is the standard approach for the local treatment of resectable metastatic disease. However, patients with liver or lung oligometastases can also be considered for tumor ablation therapy, particularly in cases that may not be optimal for resection. Ablative techniques include radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation, and electro-coagulation (irreversible electroporation). There is extensive evidence on the use of RFA as a reasonable treatment option for non-surgical candidates and for recurrent disease after hepatectomy with small liver metastases that can be treated with clear margins.
    b. Data on ablative techniques other than RFA are growing. However, in a comparison of RFA with MWA, outcomes were similar with no local tumor progression for metastases ablated with margins greater than 10 mm (A0) and a relatively better control of perivascular tumors with the use of MWA (P = .021). Similarly, two studies and a position paper by a panel of experts indicated that ablation may provide acceptable oncologic outcomes for selected patients with small liver metastases that can be ablated with sufficient margins. In the same way, a 2018 systematic review confirmed that MWA provides oncologic outcomes similar to resection. Several publications have indicated that the significance of margin creation is particularly important for RAS-mutant metastases.
    c. Yttrium-90
        i. When hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume, approaches using preoperative portal vein

embolization, staged liver resection, or yttrium-90 radioembolization can be considered. Arterially directed catheter therapy, and in particular yttrium-90 microsphere selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases

2) **Morris 2023**, ASCO guideline on the treatment of metastatic colorectal cancer
    a. Cytoreductive surgery (CRS) plus systemic chemotherapy may be recommended for selected patients with colorectal peritoneal metastases (Type: Evidence-based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Weak).
        i. This recommendation applies to patients who have been deemed amenable to complete resection of colorectal peritoneal metastases, regardless of previous treatment, and who have no extraperitoneal metastases.
    b. Surgery with or without perioperative chemotherapy should be offered to patients with mCRC who are candidates for potentially curative resection of liver metastases (Type: Evidence-based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Weak).

Ovarian cancer

1) **NCCN 2.2023** Ovarian Cancer
    a. Does not mention treatment of liver metastases

Neuroendocrine tumors

1) **NCCN 1.2023** Neuroendocrine and adrenal tumors
    a. For patients with locoregional advanced, liver-predominant, progressive disease or patients with poorly controlled carcinoid syndrome, liver-directed therapies are recommended, mainly with the palliative goals of extending life and relieving hormonal symptoms
    b. Cytoreductive surgery or ablative therapies such as radiofrequency ablation (RFA) or cryoablation may be considered if near-complete treatment of tumor burden can be achieved (category 2B). Ablative therapy in this setting is non-curative. Data on the use of these interventions are emerging. For unresectable liver metastases, hepatic regional therapy (arterial embolization, chemoembolization, or radioembolization [category 2B]) is recommended. No single modality of embolization therapy has been shown to be superior to another, but there is a difference in both long-term and short-term toxicities among the different modalities
    c. Liver-directed therapy consists of four categories of treatment:
        i. Surgical resection (which may include intraoperative thermal ablation of lesions);
        ii. Hepatic arterial embolization, including bland transarterial embolization [TAE], chemoembolization [TACE], and radioembolization [TARE]
        iii. Percutaneous thermal ablation
        iv. RT (SBRT/SABR)
    d. Percutaneous thermal ablation, often using microwave energy (radiofrequency and cryoablation are also acceptable), can be considered for oligometastatic liver disease, generally up to four lesions each smaller than 3 cm. Feasibility considerations include safe percutaneous imaging-guided approach to the target lesions, and proximity to vessels, bile ducts, or adjacent non-target structures that may require hydro- or aero-dissection for displacement.

Treatment of Liver Metastases

e. Cytoreductive surgery of >90% of metastatic disease may provide symptomatic relief, prevent future symptoms, and improve progression-free survival for patients with functioning tumors. This strategy is particularly appropriate for patients with relatively indolent metastatic small bowel NETs, and less appropriate for patients in whom rapid progression of disease is expected after surgery. Patients who are symptomatic from hormonal syndromes, such as carcinoid syndrome, typically derive palliation from cytoreductive surgery.
f. Liver-directed therapies (eg, liver resection, thermal ablation, chemoembolization) for hepatic metastases from NETs following pancreatoduodenectomy are associated with increased risk for cholangitis and liver abscess.

Hepatocellular carcinoma

1) **NCCN 1.2023** Hepatocellular carcinoma
    a. "In an ablative procedure, tumor necrosis can be induced either by thermal ablation (RFA or MWA) or cryoablation. Ablative procedures can be performed by percutaneous, laparoscopic, or open approaches"
    b. The evidence review included in this NCCN guideline does not include any studies or evaluation of cryoablation. It is noted that that RFA and MWA have largely replaced other ablative techniques

Other payer policies:

1) Aetna 2023

a. Aetna considers the following as medically necessary when the following criteria are met:
b. Cryosurgery, microwave, or radiofrequency ablation for members with isolated colorectal cancer liver metastases or isolated hepatocellular cancer who are not candidates for open surgical resection when the selection criteria specified below are met. Members must fulfill *all* of the following criteria. Particular emphasis should be placed on criteria 2 and 3, which ensure that cryosurgery, microwave, or radiofrequency ablation is performed with curative intent.
    i. Members must either have hepatic metastases from a colorectal primary cancer or have a hepatocellular cancer; *and*
    ii. Members must have isolated liver disease. Members with nodal or extra-hepatic systemic metastases are not considered candidates for these procedures; *and*
    iii. All tumors in the liver, as determined by pre-operative imaging, would be potentially destroyed by cryotherapy, microwave, or radiofrequency ablation; *and*
    iv. Because open surgical resection is the preferred treatment, members must be unacceptable open surgical candidates due to the location or extent of the liver disease or due to co-morbid conditions such that the member is unable to tolerate an open surgical resection; *and*
    v. Liver lesions must be 4 cm or less in diameter and occupy less than 50 % of the liver parenchyma. Lesions larger than this may not be adequately treated by these procedures.
c. Aetna considers cryosurgery, microwave, or radiofrequency ablation of hepatic lesions experimental and investigational when these criteria are not met.

d. The following procedures are considered experimental and investigational because the effectiveness of these approaches has not been established
    i. Cryosurgery, microwave, or radiofrequency ablation as a treatment of hepatic metastases from non-colonic primary cancers;
    ii. Cryosurgical, microwave or radiofrequency ablation as a palliative treatment of either hepatic metastases from colorectal cancer or hepatocellular cancer

2) **Anthem BCBS 2023**, Locoregional Techniques for Treating Primary and Metastatic Liver Malignancies
    a. Medically Necessary:
        i. *Treatment of Hepatic Tumors (Primary or Metastatic)*
            1. Any of the following locally ablative techniques are considered medically necessary for individuals with *any* of the following conditions when *all* of the criteria below have been met:
                a. Techniques
                    i. Cryosurgical ablation; **or**
                    ii. Microwave ablation (MWA); **or**
                    iii. Percutaneous ethanol injection (PEI); **or**
                    iv. Radiofrequency (RFA)
                    and
                b. Conditions
                    i. Hepatocellular carcinoma; **or**
                    ii. Liver metastases from colorectal cancer; **or**
                    iii. Functioning neuroendocrine tumors
                    and
                c. Criteria
                    i. A poor candidate for surgical resection or unwilling to undergo surgical resection; **and**
                    ii. Each lesion measures no more than 5 cm in diameter; **and**
                    iii. No or minimal extra-hepatic metastases; **and**
                    iv. All foci of disease are amenable to ablative therapy or surgical resection.

Expert input:

Dr. Brett Sheppard, OHSU surgery

I just wanted to be sure we are reviewing metastatic disease to the liver (CRC, PNET) [Colorectal cancer, pancreatic/small bowel neuroendocrine tumors] and differentiate this from primary HCC or intra-hepatic cholangiocarcinoma.

For common metastatic disease to the liver (CRC, PNET), I would concur with you that OHP would be providing the best care possible by funding surgical resection and/or ablation (most of us have moved to microwave, some irreversible electroporation).

There is good data that shows even for non-functional PNET and NET that if they are able to have surgical debulking of at least 75% of their tumor they will reap a significant survival benefit.

Treatment of Liver Metastases

This can be completed with surgery +/- microwave ablation (MWA). It would be something to consider for our OHP patients.

I concur with you that cryoablation does not need to be covered. MWA can now generally accomplish the same and has a lower side effect profile than cryoablation and may be less expensive as procedure time may be shorter.

I agree with the revised guidelines. If you agree, after appropriate literature search, about my statement in regards to non-functional PNEt/NET then they would need to be modified

Treatment of Liver Metastases

HERC staff summary:

Expert guidelines recommend various interventions to treat liver metastases for colorectal tumors when a patient is not a good candidate for surgical resection. Such interventions are recommended when there are no metastases outside of the liver. Ablative techniques include radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation, and electro-coagulation (irreversible electroporation). The best evidence for ablative techniques per NCCN is for RFA and MWA.

NCCN mentions ablation of liver metastases from neuroendocrine cancer as a "can be considered" option, noting that it is a palliative rather than curative treatment. However, NCCN mentions ablation of such liver metastases as being helpful for patients who are symptomatic from hormonal syndromes caused by the neuroendocrine tumor. Local experts recommend coverage for neuroendocrine tumors liver metastases that are functional (i.e. producing hormones that are causing symptoms).

The evidence for percutaneous cryotherapy of liver metastases is poor, consisting only of relatively small prospective and retrospective cohorts. There is one small RCT on any type of cryoablation of liver metastases (cryoresection, cryoreduction, croyextirpation).

Private insurers cover treatment of certain types of cancer with liver metastases (colorectal, with some covering neuroendocrine as well) with cryosurgery, microwave, or radiofrequency ablation. This coverage is limited to metastatic disease isolated to the liver when the patient is a poor candidate for surgical resection.

HERC staff recommend clarifying GN78. First, the intent appears to be to allow surgical resection of any type of liver metastases (any primary tumor) as long as the metastases are isolated to the liver. Second, additional ablative procedures (radiofrequency ablation, microwave ablation) should be allowed only for hepatocellular carcinoma, colorectal cancer metastatic to the liver, and functional neuroendocrine tumors metastatic to the liver. In the case of metastatic disease, coverage should be limited to patients who have only liver metastases present and only when the patient is not a candidate for surgical resection.

HERC staff recommend continuing non-coverage of percutaneous cryoablation, and adding surgical cryoablation to the line 662/GN173 entry as the evidence of effectiveness is poor. NCCN notes that RFA and MWA are generally considered the treatments of choice for ablative procedures for hepatocellular carcinoma and colorectal cancer metastatic in the liver.

Yttrium-90 treatment only has high level of evidence of effectiveness for treatment of HCC. NCCN includes as an option in certain clinical scenarios with metastatic colorectal cancer.

HERC staff recommendations:

1) Remove the following CPT codes from line 315 CANCER OF LIVER and add to line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
    a. CPT 47371 Laparoscopy, surgical, ablation of 1 or more liver tumor(s); cryosurgical
    b. CPT 47381 Ablation, open, of 1 or more liver tumor(s); cryosurgical
2) Modify the GN173 entry regarding cryosurgical treatment of liver tumors as shown below
3) Modify GN78 as shown below

Treatment of Liver Metastases

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

Line 662

The following Interventions are prioritized on Line 662 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
47371, 47381, 47383	Ablation, 1 or more liver tumor(s), percutaneous, cryoablation	No evidence of effectiveness for both hepatocellular carcinoma and metastatic disease	~~November, 2014~~ September 2023

GUIDELINE NOTE 78, HEPATIC METASTASES

Line 315

~~ICD-10-CM C78.7~~ Hepatectomy/resection (CPT codes 47120, 47122,47125 or 47130) of hepatic metastases (ICD-10-CM C22.9 Or C78.7) are included on this line only when there are no other extrahepatic metastases.

A) ~~Treatment of the primary tumor is covered on a funded line in accordance with the criteria in Guideline Note 12 PATIENT-CENTERED CARE OF ADVANCED CANCER;~~
B) ~~There are no other extrahepatic metastases; and,~~
C) ~~The only treatment covered is hepatectomy/resection of liver (CPT codes 47120, 47122,47125 or 47130).~~

Microwave and radiofrequency ablation (CPT 47340, 47389, 47382) are included on this line only when ALL of the following criteria are met:

A) Treatment is for colorectal cancer liver metastases, functioning neuroendocrine tumors or hepatocellular cancer; AND
B) There are no extrahepatic metastases; AND
C) The patient is not a candidate for open surgical resection due to the location or extent of the liver disease or due to co-morbid conditions such that the member is unable to tolerate an open surgical resection; AND
D) All tumors in the liver, as determined by pre-operative imaging, would be potentially destroyed by cryotherapy, microwave, or radiofrequency ablation; AND
E) Liver lesions must be 4 cm or less in diameter and occupy less than 50 % of the liver parenchyma.

Yttrium-90 therapy (CPT 79445) is only covered for treatment of hepatocellular carcinoma as specified in GUIDELINE NOTE 185, YTTRIUM-90 THERAPY.

Cochrane Library

Cochrane Database of Systematic Reviews

Cryotherapy for liver metastases (Review)

Bala MM, Riemsma RP, Wolff R, Pedziwiatr M, Mitus JW, Storman D, Swierz MJ, Kleijnen J

Bala MM, Riemsma RP, Wolff R, Pedziwiatr M, Mitus JW, Storman D, Swierz MJ, Kleijnen J.
Cryotherapy for liver metastases.
Cochrane Database of Systematic Reviews 2019, Issue 7. Art. No.: CD009058.
DOI: 10.1002/14651858.CD009058.pub3.

www.cochranelibrary.com

WILEY

[Intervention Review]

Cryotherapy for liver metastases

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Editorial group: Cochrane Hepato-Biliary Group.
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ABSTRACT

Background

The liver is affected by two of the most common groups of malignant tumours: primary liver tumours and liver metastases from colorectal carcinoma. Liver metastases are significantly more common than primary liver cancer and long-term survival rates reported for patients after radical surgical treatment is approximately 50%. However, R0 resection (resection for cure) is not feasible in the majority of patients. Cryotherapy is performed with the use of an image-guided cryoprobe which delivers liquid nitrogen or argon gas to the tumour tissue. The subsequent process of freezing is associated with formation of ice crystals, which directly damage exposed tissue, including cancer cells.

Objectives

To assess the beneficial and harmful effects of cryotherapy compared with no intervention, other ablation methods, or systemic treatments in people with liver metastases.

Search methods

We searched The Cochrane Hepato-Biliary Group Controlled Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE Ovid, Embase Ovid, and six other databases up to June 2018.

Selection criteria

Randomised clinical trials assessing beneficial and harmful effects of cryotherapy and its comparators for liver metastases, irrespective of the location of the primary tumour.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. We extracted information on participant characteristics, interventions, study outcomes, and data on the outcomes important for our review, as well as information on the design and methodology of the trials. Two review authors independently assessed risk of bias in each study. One review author performed data extraction and a second review author checked entries.

The trial did not provide information on funding.

Key results

The trial was at high risk of bias. The participants were followed for up to 10 years (minimum five months). The trial reported that the mortality at 10 years was 81% (51/63) in the cryotherapy group and 92% (55/60) in the conventional surgery group. We judged the evidence as low-certainty evidence. We found no evidence of a difference in proportion of participants with recurrence of the malignancy in the liver: 86% (54/63) of the participants in the cryotherapy group and 95% (57/60) of the participants in the conventional surgery group developed a new malignancy (low-certainty evidence). The frequency of reported complications was similar between the cryotherapy group and the conventional surgery group, except for postoperative pain. Both insignificant and pronounced pain were reported to be more common in the cryotherapy group while intense pain was reported to be more common in the conventional surgery group. However, it was not reported whether there was any evidence of a difference. The frequency of unwanted effects (adverse events or complications) was mostly similar in both groups, but pain intensity and frequency seemed to differ between the groups. There were no intervention-related mortality or bile leakages. The trial did not provide data on quality of life; cancer mortality, and time to progression of liver metastases.

Reliability of the evidence

The evidence for the effectiveness of cryotherapy versus conventional surgery in people with liver metastases is of low certainty. We are uncertain about our estimate and cannot determine whether cryotherapy compared with conventional surgery is beneficial or harmful. We found no evidence for the benefits or harms of cryotherapy compared with no intervention, or versus systemic treatments.

PLOS ONE

RESEARCH ARTICLE

Survival outcomes and quality of life after percutaneous cryoablation for liver metastasis: A systematic review and meta-analysis

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Competing interests: The authors have declared that no competing interests exist.

Abstract

Background

Liver metastasis is present in a wide range of malignancies, with colorectal cancer as the most common site. Several minimally invasive treatments have been suggested for managing hepatic metastases, and cryoablation is among them, yet not widely used. In this systematic review, we aimed to assess the effectiveness of percutaneous cryoablation in all types of liver metastases.

Methods

A systematic search was performed in international databases, including PubMed, Scopus, Embase, and Web of Science, to find relevant studies reporting outcomes for percutaneous cryoablation in liver metastasis patients. In addition to baseline features such as mean age, gender, metastasis origin, and procedure details, procedure outcomes, including overall survival, local recurrence, quality of life (QoL), and complications, were extracted from the studies. Random-effect meta-analysis was performed to calculate the mean difference (MD) and 95% confidence interval for comparison of QoL.

Results

We screened 2131 articles. Fifteen studies on 692 patients were included. Mean overall survival ranged from 14.5–29 months. The rate of local recurrence in the included studies ranged from 9.4% to 78%, and local control progression-free survival ranged from 1 to 31 months. The total QoL decreased one week after the cryoablation procedure (-3.08 [95% Confidence interval: -4.65, -1.50], p-value <0.01) but increased one month (5.69 [3.99,

7.39], p-value <0.01) and three months (3.75 [2.25, 5.24], p-value <0.01) after the procedure.

Conclusion

Cryoablation is an effective procedure for the treatment of liver metastases, especially in cases that are poor candidates for liver resection. It could significantly improve QoL with favorable local recurrence.

1. Introduction

The liver is a common site for metastasis from various malignancies such as colorectal cancer, lung cancer, melanoma, and breast cancer, among which colorectal cancer is the most common primary site [1]. In the United States, about 5.1% of all patients diagnosed with malignancy have synchronous liver metastases at the time of diagnosis [2], while it reaches 50% in patients with colorectal cancer origin [3]. Several clinical modalities have been established for liver metastases treatment, including liver resection, systemic and local chemotherapy, and radiotherapy [4]. While liver resection is still the main curative option for colorectal liver metastases [5], this is not the case for many others, such as breast cancer and esophageal cancer [6,7].

In recent years, interventional oncology has become very popular for managing primary and secondary liver malignancies due to its ability to improve survival, reduce tumor burden, and low complication rate [8]. So, the emerging role of interventional oncology as a treatment alone, as a bridge to transplantation, or in association with other approaches could not be denied [9,10].

Thermal ablation, including radiofrequency ablation (RFA) or microwave ablation (MWA), is the most popular local minimally invasive method with many publications and studies. However, cold ablation is less considered in the liver and is not extensively available. Percutaneous cryoablation is in situ destruction of tumor cells with low temperatures. Mechanistically, cellular dehydration, protein denaturation, and microcirculatory failure in thawing and freezing cycles are the main pathways the cryoablation affects the tumor [11]. The current method of cryoablation is the administration of probes with the use of circulating cooled fluid or gas, such as nitrogen or argon, which then expands into a gas, creating low temperatures, including the Joule-Thomson effect [12]. It was first suggested that cryoablation might only be used in cases of liver metastases from colorectal cancer; however, several other studies have assessed the procedure's effects in other types of metastases [13–15]. Many of these studies have shown the efficacy of cryoablation in improving survival and quality of life (QoL). To date, there is no systematic review investigating the role of cryoablation in liver metastases from different origins. In the present systematic review, we aimed to investigate the effectiveness of percutaneous cryoablation in treating liver metastases through a systematic search in the literature and finding relevant studies.

2. Methods and materials

This review was conducted in compliance with the review protocol registered on PROSPERO, 2023 CRD42023390082. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement was followed in this study [16]. An ethics statement is not applicable because this study is based exclusively on published literature.

ASCO special articles

Treatment of Metastatic Colorectal Cancer: ASCO Guideline

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abstract

PURPOSE To develop recommendations for treatment of patients with metastatic colorectal cancer (mCRC).

METHODS ASCO convened an Expert Panel to conduct a systematic review of relevant studies and develop recommendations for clinical practice.

RESULTS Five systematic reviews and 10 randomized controlled trials met the systematic review inclusion criteria.

RECOMMENDATIONS Doublet chemotherapy should be offered, or triplet therapy may be offered to patients with previously untreated, initially unresectable mCRC, on the basis of included studies of chemotherapy in combination with anti–vascular endothelial growth factor antibodies. In the first-line setting, pembrolizumab is recommended for patients with mCRC and microsatellite instability-high or deficient mismatch repair tumors; chemotherapy and anti–epidermal growth factor receptor therapy is recommended for microsatellite stable or proficient mismatch repair left-sided treatment-naive *RAS* wild-type mCRC; chemotherapy and anti–vascular endothelial growth factor therapy is recommended for microsatellite stable or proficient mismatch repair *RAS* wild-type right-sided mCRC. Encorafenib plus cetuximab is recommended for patients with previously treated *BRAF* V600E–mutant mCRC that has progressed after at least one previous line of therapy. Cytoreductive surgery plus systemic chemotherapy may be recommended for selected patients with colorectal peritoneal metastases; however, the addition of hyperthermic intraperitoneal chemotherapy is not recommended. Stereotactic body radiation therapy may be recommended following systemic therapy for patients with oligometastases of the liver who are not considered candidates for resection. Selective internal radiation therapy is not routinely recommended for patients with unilobar or bilobar metastases of the liver. Perioperative chemotherapy or surgery alone should be offered to patients with mCRC who are candidates for potentially curative resection of liver metastases. Multidisciplinary team management and shared decision making are recommended. Qualifying statements with further details related to implementation of guideline recommendations are also included.

Additional information is available at www.asco.org/gastrointestinal-cancer-guidelines.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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July 15, 2022.

INTRODUCTION

Colorectal cancer (CRC) is the third most common type of cancer diagnosed worldwide.[1] Almost 150,000 new cases and more than 50,000 deaths from CRC are reported each year in the United States.[2] In recent decades, the overall incidence of CRC has decreased among older adults because of screening and lifestyle factors; however, at the same time, incidence is increasing among younger adults.[3] The 5-year relative overall survival (OS) for patients with metastatic colorectal cancer (mCRC) is approximately 15%.[4] Approximately 33% of patients with CRC will develop metastases either at presentation or follow-up.[5] Evaluating treatment options is complex because of the heterogeneity of the patient population, including different molecular subtypes. Treatment has included conventional fluorouracil (FU)–based chemotherapy, and more recently, targeted therapies have been developed for specific molecular subtypes and primary tumor sidedness.[6] This guideline provides a review of the evidence for areas of uncertainty in the treatment of mCRC, including indications for targeted therapy, and treatment options for oligometastatic and liver-limited disease.

National Institute for Health and Care Excellence

Final

Colorectal cancer (update)

[D2a] Treatment for metastatic colorectal cancer in the liver amenable to treatment with curative intent

NICE guideline NG151

Evidence reviews

January 2020

Final

Developed by the National Guideline Alliance part of the Royal College of Obstetricians and Gynaecologists

Foot and Toenail Care for Patients in Facilities

Plain Language Summary:

Coverage question: Should OHP cover nail and foot care for people who live in nursing homes?

Should OHP cover this treatment? Certain conditions should be covered because active fungal infections in a nursing home can be passed from patient to patient and is a public health issue.

Coverage Question: Should foot and toenail care be covered for patients in skilled nursing and similar facilities?

Question source: Dr. Shazad Buksh, podiatrist

Background: HERC staff recently conducted a community listening session. One issue that was raised was regarding lack of coverage for foot and toenail care for patients living in nursing facilities. This issue was also raised last year when staff met with advocates for aging services.

From the June 2023 HERC staff listening session:

> Dr. Buksh, a podiatrist, spoke about lack of access to foot and nail care in skilled nursing facilities, rehabilitation facilities and similar settings. He spoke about the importance of treating nail conditions such as onychomycosis in these settings to both prevent spread and reduce the risk of secondary infections and subsequent adverse outcomes. Dr. Buksh requested consideration of coverage for toenail care, toenail biopsies and lab testing, antifungal medications, and toenail debridement for patients in care facilities. Dr. Buksh argued that fungal infections in facilities can be passed from patient to patient, making non-coverage of treatment a public health issue. Non-treatment also leads to increased risk of abscesses, bleeding, and cellulitis. He specifically was interested in coverage of patients in skilled nursing and rehabilitation facilities, but also noted that this is a problem in homeless shelters and other group settings. Specific codes mentioned for coverage include ICD-0-CM B35.1 (Tinea unguium), toenail biopsy and debridement procedures, and medications such as topical and oral antifungals.

Currently, foot care is covered for patients at high risk for foot complications from diabetes, neuropathy, and similar conditions. Tinea unguium (toenail fungus) is currently only on an uncovered line.

In conversations with other parts of HSD, HERC staff were informed that medications and procedures can be evaluated and approved based on coding indicating place of service, such as a skilled nursing facility. Such evaluation would need to be part of a prior authorization process. There are ICD-10-CM codes such as Y92.10 (Unspecified residential institution as the place of occurrence of the external cause) that could be used as a secondary code to allow automation of claims if that is preferred.

Foot and Toenail Care for Patients in Facilities

This issue was part of the early packet for additional public comment. As part of that process, coverage of dystrophic nails (ICD-10-CM L60.2 and L60.3) was raised as other conditions that cause pain, difficulty ambulation, and increased risk of infection.

Previous HSC/HERC reviews:

Nail care for patients in facilities has not been discussed in at least the past 10 years

Current Prioritized List/Coverage status:

Line:	**165**
Condition:	PREVENTIVE FOOT CARE IN HIGH-RISK PATIENTS
Treatment:	MEDICAL AND SURGICAL TREATMENT OF TOENAILS AND HYPERKERATOSES OF FOOT
ICD-10:	E08.40-E08.42,E08.51-E08.52,E08.621,E09.40-E09.42,E09.51-E09.52,E09.621,E10.40-E10.42,E10.51-E10.52,E10.621,E11.40-E11.42,E11.49-E11.59,E11.621,E11.628,E13.40-E13.42,E13.44,E13.51-E13.52,E13.621,G60.0-G60.8,G61.0-G61.1,G61.81-G61.9,G62.0-G62.2,G62.81-G62.9,I70.201-I70.299,Z86.31
CPT:	11055-11057,11719-11732,11750,98966-98972,99051,99060,99070,99078,99202-99215,99341-99350,99366,99374,99375,99381-99404,99411-99417,99421-99449,99451,99452,99487-99491,99495-99498,99605-99607
HCPCS:	G0068,G0071,G0088,G0090,G0245-G0250,G0318,G0323,G0463,G0466,G0467,G0490,G0511,G2012,G2211,G2214,G2251-G3003

ICD-10-CM B35. 1 (Tinea unguium) is on line 489 DERMATOPHYTOSIS OF NAIL, GROIN, AND FOOT AND OTHER DERMATOMYCOSIS. This code is used for onychomycosis

ICD-10-CM L60.3 (Nail dystrophy) and L60.2 (Onychogryphosis) are on line 587 DISEASE OF NAILS, HAIR AND HAIR FOLLICLES

CPT 11055-11057 (Paring or cutting of benign hyperkeratotic lesion (eg, corn or callus)) are on lines 165,235,555,589,613,625

CPT 11720-11721 (Debridement of nails) are on lines 137 OPPORTUNISTIC INFECTIONS IN IMMUNOCOMPROMISED HOSTS; CANDIDIASIS OF STOMA; PERSONS RECEIVING CONTINUOUS ANTIBIOTIC THERAPY, 165 PREVENTIVE FOOT CARE IN HIGH-RISK PATIENTS, 489 ERMATOPHYTOSIS OF NAIL, GROIN, AND FOOT AND OTHER DERMATOMYCOSIS, 587 DISEASE OF NAILS, HAIR AND HAIR FOLLICLES

CPT 11730-11732 (Avulsion of pail plate, partial or complete) are on lines 165, 205, 207,289,489,587

CPT 11750 (Excision of nail and nail matrix, partial or complete (eg, ingrown or deformed nail), for permanent removal) is on lines 165,205,207,489,587

Foot and Toenail Care for Patients in Facilities

CPT 11755 (Biopsy of nail unit (eg, plate, bed, matrix, hyponychium, proximal and lateral nail folds) (separate procedure)) is on line 587 DISEASE OF NAILS, HAIR AND HAIR FOLLICLES

HCPCS G0127 (Trimming of dystrophic nails, any number) is listed as never reviewed

Evidence:

1) **Leung 2020**, review of onychomycosis
    a. The diagnosis can be confirmed by direct microscopic examination with a Potassium Hydroxide (KOH) wet-mount preparation, histopathologic examination of the trimmed affected nail plate with a Periodic-Acid-Schiff (PAS) stain, fungal culture, or Polymerase Chain Reaction (PCR) assays. The ideal test would identify the fungus and the species, determine its viability, be easy to perform with rapid result and low cost, and be highly specific and sensitive
    b. Treatment options include oral antifungal therapy, topical antifungal therapy, laser therapy, photodynamic therapy, and surgical avulsion (e.g. very thick and chronic fungal nail).
    c. There is an increased risk for bacterial infections such as cellulitis and paronychia, especially in immunocompromised individuals including diabetics [36, 88]. Severe onychomycosis may interfere with standing, walking, nail function, and daily activities [11, 53]. The condition, if left untreated, may cause discomfort, pain, paresthesia, nail deformities such as transverse over-curvature, difficulties in trimming thick nail plates, difficulties in fitting shoes, and low self-esteem

Other payer policies:

1) CMS Routine Foot Care and Debridement of Nails 2021
    a. The Medicare program generally does not cover routine foot care. However, this determination outlines the specific conditions for which coverage may be present.
    b. The following services are considered to be components of routine foot care, regardless of the provider rendering the service:
        i. Cutting or removal of corns and calluses;
        ii. Clipping, trimming, or debridement of nails, including debridement of mycotic nails;
        iii. Shaving, paring, cutting or removal of keratoma, tyloma, and heloma;
        iv. Non-definitive simple, palliative treatments like shaving or paring of plantar warts which do not require thermal or chemical cautery and curettage;
        v. Other hygienic and preventive maintenance care in the realm of self care, such as cleaning and soaking the feet and the use of skin creams to maintain skin tone of both ambulatory and bedridden patients;
        vi. Any services performed in the absence of localized illness, injury, or symptoms involving the foot.
    c. Medicare payment may be made for routine foot care when the patient has a systemic disease, such as metabolic, neurologic, or peripheral vascular disease, of sufficient severity that performance of such services by a nonprofessional person would put the

patient at risk (for example, a systemic condition that has resulted in severe circulatory embarrassment or areas of desensitization in the patient's legs or feet).

d. Treatment of mycotic nails may be covered under the exceptions to the routine foot care exclusion. The class findings, outlined below, or the presence of qualifying systemic illnesses causing a peripheral neuropathy, must be present. Payment may be made for the debridement of a mycotic nail (whether by manual method or by electrical grinder) when definitive antifungal treatment options have been reviewed and discussed with the patient at the initial visit and the physician attending the mycotic condition documents that the following criteria are met:
    i. In the absence of a systemic condition, the following criteria must be met:
        1. In the case of ambulatory patients there exists:
            a. Clinical evidence of mycosis of the toenail, and
            b. Marked limitation of ambulation, pain, and/or secondary infection resulting from the thickening and dystrophy of the infected toenail plate.
        2. In the case of non-ambulatory patients there exists:
            a. Clinical evidence of mycosis of the toenail, and
            b. The patient suffers from pain and/or secondary infection resulting from the thickening and dystrophy of the infected toenail plate.

e. In addition, procedures for treating toenails are covered for the following:
    i. Onychogryphosis (defined as long-standing thickening, in which typically a curved hooked nail (ram's horn nail) occurs), and there is marked limitation of ambulation, pain, and/or secondary infection where the nail plate is causing symptomatic indentation of or minor laceration of the affected distal toe; and/or
    ii. Onychauxis (defined as a thickening (hypertrophy) of the base of the nail/nail bed) and there is marked limitation of ambulation, pain, and/or secondary infection that causes symptoms.

f. The following physical and clinical findings, which are indicative of severe peripheral involvement, must be documented and maintained in the patient record, in order for routine foot care services to be reimbursable.
    i. <u>Class A findings</u>
    Non-traumatic amputation of foot or integral skeletal portion thereof
    ii. <u>Class B findings</u>
    Absent posterior tibial pulse
    Advanced trophic changes as evidenced by any three of the following:
        1. hair growth (decrease or increase)
        2. nail changes (thickening)
        3. pigmentary changes (discoloring)
        4. skin texture (thin, shiny)
        5. skin color (rubor or redness);and
        6. Absent dorsalis pedis pulse
    iii. <u>Class C findings</u>
    Claudication
    Temperature changes (e.g., cold feet)
    Edema

Paresthesias (abnormal spontaneous sensations in the feet)
Burning

g. The presumption of coverage may be applied when the physician rendering the routine foot care has identified:
    i. A Class A finding
    ii. Two of the Class B findings; or
    iii. One Class B and two Class C findings.
h. Note: Benefits for routine foot care are also available for patients with peripheral neuropathy involving the feet, but without the vascular impairment outlined in Class B findings. The neuropathy should be of such severity that care by a non-professional person would put the patient at risk. If the patient has evidence of neuropathy but no vascular impairment, the use of class findings modifiers is not necessary. This condition would be represented by the appropriate ICD-10-CM code being included on the claim.

2) Aetna 2023

a. Routine foot care is not covered under most of Aetna plans. Please check benefit plan descriptions for details. Under plans that exclude routine foot care, foot care is considered non-routine and covered only in the following circumstances when medically necessary:
    i. The non-professional performance of the service would be hazardous for the member because of an underlying condition or disease; *or*
    ii. Routine foot care is performed as a necessary and integral part of an otherwise covered service (e.g., debriding of a nail to expose a subungual ulcer, or treatment of warts); *or*
    iii. Debridement of mycotic nails is undertaken when the mycosis/dystrophy of the toenail is causing secondary infection and/or pain, which results or would result in marked limitation of ambulation and require the professional skills of a provider.

3) Cigna 2023

a. Coverage for routine foot care, including the paring and removing of corns and calluses or trimming of nails, varies across plans. Please refer to the customer's benefit plan document for coverage details. Foot care services are considered medically necessary when EITHER of the following criteria is met:
    i. The foot care services that are associated with systemic conditions that are significant enough to result in severe circulatory insufficiency and/or areas of desensitization in the lower extremities, including, but not limited to, ANY of the following:
        1. diabetes mellitus
        2. peripheral vascular disease
        3. peripheral neuropathy
    ii. Evaluation/debridement of mycotic nails, in the absence of a systemic condition, when BOTH of the following conditions are met:
        1. There is pain or secondary infection resulting from the thickening and dystrophy of the infected toenail plate.
        2. If ambulatory, there is pain to a degree that there is difficulty walking and/or abnormality of gait.

Foot and Toenail Care for Patients in Facilities

Expert input:

Dr. Chris Seuferling, podiatrist
Recommended not requiring biopsy or culture to prove a fungal infection, as typically this condition can be diagnosed clinically and the additional cost of such testing is not necessary and invasive testing caries risks.

Public Comment Disposition

Commenter	Comment	Staff response
Oregon Podiatric Medical Association Board member comments	ICD-10 codes of L60.3 [Nail dystrophy] and L60.2 [Onychogryphosis] should be included and [HCPCS] code G0127 [Trimming of dystrophic nails, any number] Rationale: • Debridement of mycotic nails is undertaken when the mycosis/dystrophy of the toenail is causing secondary infection and/or pain, which results or would result in marked limitation of ambulation and require the professional skills of a provider. • Coverage for routine foot care, including the paring and removing of corns and calluses or trimming of nails, varies across plans….. There is pain or secondary infection resulting from the thickening and dystrophy of the infected toenail plate. • If ambulatory, there is pain to a degree that there is difficulty walking and/or abnormality of gait.	Review of other payer policies finds that these diagnoses and treatment are covered for the same indications as onychomycosis. Staff have revised the recommendations in this issue to include these diagnosis and treatment codes.
Lisa Nakadate Executive Director Oregon Podiatric Medical Association	I am writing to voice the Oregon Podiatric Medical Association's support for the proposed changes to the Oregon Health Plan coverage which would allow nail care for individuals who live in skilled nursing facilities. This is a sensitive population which often lacks access to foot and nail care. Including nail coverage for our elderly patients will have a dramatic effect on their quality of life, keeping them mobile and healthy. In addition, it will help prevent the spread of infection and reduce the risk of secondary infections	Thank you for your comment

	and adverse outcomes. Having access to foot and nail care will lead to better health outcomes and healthier patients. Thank you for considering these changes to OHP coverage. We are in full support of them and appreciate the opportunity to comment.	

Foot and Toenail Care for Patients in Facilities

HERC staff summary:

Two community listening opportunities have brought up problems with lack of coverage for routine foot and toenail care for patients in nursing and other care facilities. In particular, lack of coverage for treatment of toenail fungus has been raised as an issue. Medicare allows coverage for toenail fungus, as well as for routine nail care in certain high risk patient categories. Additional public comment recommended adding coverage for dystrophic nails and onychogryphosis, which lead to pain, difficulty ambulating, and increased risk of infection. Private insurers vary on whether they have any coverage for foot related care.

HERC staff recommendations:

1) Add ICD-10-CM B35. 1 (Tinea unguium), L60.2 (Onychogryphosis), and L60.3 (Nail dystrophy) to line 165 PREVENTIVE FOOT CARE IN HIGH-RISK PATIENTS
    a. Line 165 contains CPT codes for pairing/cutting of corns and calluses, debridement of nails, and avulsion of nail plates
2) Add CPT 11755 (Biopsy of nail unit (eg, plate, bed, matrix, hyponychium, proximal and lateral nail folds) (separate procedure)) to line 165
3) Add HCPCS G0127 (Trimming of dystrophic nails, any number) to line 165
4) Adopt a new guideline regarding testing and treatment of tinea unguium and dystrophic nails as shown below

GUIDELINE NOTE XXX HIGH RISK FOOT CARE

Lines 165, 489

Foot care by a medical professional, including pairing and cutting of corns and calluses, debridement of nails, avulsion of nail plates, trimming of dystrophic nails, and biopsy of nails, is included on line 165 only when:

1) The patient is at high risk for complications from nail and foot problems due to a systemic condition that has resulted in severe circulatory insufficiency and/or areas of desensitization in the lower extremities; OR
2) The patient resides in a skilled nursing facility, rehabilitation facility, group home or similar institutional setting.

Evaluation for and treatment of tinea unguium (ICD-10-CM B35.1) including biopsy of nails, nail paring, and treatment with topical or oral antifungal medications is included on line 165 only when:

1) The patient is in one of the two high risk groups identified above; AND
2) There is clinical evidence of mycosis of the toenail; AND
3) The patient has documented marked limitation of ambulation, pain, and/or secondary bacterial infection resulting from the thickening and dystrophy of the infected toenail plate.

Otherwise, evaluation and treatment of tinea unguium is included on line 489.

Recent Patents on Inflammation & Allergy Drug Discovery 2020, *14*, 32-45

REVIEW ARTICLE

Onychomycosis: An Updated Review

Alexander K.C. Leung[1,*], Joseph M. Lam[2], Kin F. Leong[3], Kam L. Hon[4], Benjamin Barankin[5], Amy A.M. Leung[6] and Alex H.C. Wong[7]

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Abstract: ***Background***: Onychomycosis is a common fungal infection of the nail.

Objective: The study aimed to provide an update on the evaluation, diagnosis, and treatment of onychomycosis.

Methods: A PubMed search was completed in Clinical Queries using the key term "onychomycosis". The search was conducted in May 2019. The search strategy included meta-analyses, randomized controlled trials, clinical trials, observational studies, and reviews published within the past 20 years. The search was restricted to English literature. Patents were searched using the key term "onychomycosis" in www.freepatentsonline.com.

Results: Onychomycosis is a fungal infection of the nail unit. Approximately 90% of toenail and 75% of fingernail onychomycosis are caused by dermatophytes, notably *Trichophyton mentagrophytes* and *Trichophyton rubrum*. Clinical manifestations include discoloration of the nail, subungual hyperkeratosis, onycholysis, and onychauxis. The diagnosis can be confirmed by direct microscopic examination with a potassium hydroxide wet-mount preparation, histopathologic examination of the trimmed affected nail plate with a periodic-acid-Schiff stain, fungal culture, or polymerase chain reaction assays. Laboratory confirmation of onychomycosis before beginning a treatment regimen should be considered. Currently, oral terbinafine is the treatment of choice, followed by oral itraconazole. In general, topical monotherapy can be considered for mild to moderate onychomycosis and is a therapeutic option when oral antifungal agents are contraindicated or cannot be tolerated. Recent patents related to the management of onychomycosis are also discussed.

Conclusion: Oral antifungal therapies are effective, but significant adverse effects limit their use. Although topical antifungal therapies have minimal adverse events, they are less effective than oral antifungal therapies, due to poor nail penetration. Therefore, there is a need for exploring more effective and/or alternative treatment modalities for the treatment of onychomycosis which are safer and more effective.

ARTICLE HISTORY

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Keywords: Dermatophytes, itraconazole, nail discoloration, onychauxis, onycholysis, subungual hyperkeratosis, terbinafine.

1. INTRODUCTION

Onychomycosis is an infection of the nail unit caused by fungi (dermatophytes, non-dermatophyte molds, and yeasts), presenting with discoloration of the nail, onycholysis, and nail plate thickening [1, 2]. Any component of the nail unit, including the nail plate, nail matrix, and nail bed can be affected [3]. The term "onychomycosis" is derived from the Greek words "*onyx*" meaning nail and "*mykes*" meaning fungus [4]. Onychomycosis is the most common disorder affecting the nail unit and accounts for at least 50% of all nail diseases [2, 5, 6]. Laboratory confirmation of the clinical diagnosis of onychomycosis prior to initiating treatment is cost effective and is recommended [5]. In recent years, newer

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2212-2710/20 $65.00+.00

Central Auditory Function Testing

Plain Language Summary:

Coverage question: Should OHP cover testing for a condition that makes it difficult for a person to understand speech and follow instructions, especially when there is a lot of noise around.

Should OHP cover this treatment? No. The problem is a bit unclear, and even the experts can't decide on a consistent way to identify it. There are no widely accepted tests, and there are no medications for this condition. Other health plans are not covering this condition.

Coverage Question: Should evaluation of central auditory function be covered?

Question source: Holly Jo Hodges, CCO medical director

Background: According to the American Speech-Language Hearing Association (ASHA), central auditory processing disorder (CAPD), also known as auditory processing disorder, refers to difficulties in the perceptual processing of auditory information in the central nervous system (CNS). CAPD is a complex and heterogeneous group of auditory-specific disorders, usually associated with a range of listening and learning deficits. Children or adults suspected of CAPD may exhibit a variety of listening and related complaints such as difficulty understanding speech in noisy environments, following directions, and discriminating (or telling the difference between) similar-sounding speech sounds.

The diagnosis, management, and even the existence of a modality-specific dysfunction remains controversial. At this time, there is no universally accepted method of screening for CAPD. No pharmacologic agent has been demonstrated as effective specifically for CAPD. Interventions for CAPD focuses on improving the quality of the acoustic signal and the listening environment, improving auditory skills, and enhancing utilization of metacognitive and language resources.

Previous HSC/HERC reviews:

Only one previous review of central auditory function testing was found.

HOSC January 2005

> 92620/92621 Evaluation of central auditory function: Has been covered for years, but response from expert regarding why/when it is used, states they are no longer doing this test. No response from person question referred to. Per Marsha Becker-Meier, old code rarely used.
>
> Action: Add to non-OHP services list

No discussion was found related to the diagnosis H93.25 (Central auditory processing disorder) in any minutes from HSC/HOSC or VBBS/HERC.

Central Auditory Function Testing

Current Prioritized List/Coverage status:

ICD-10-CM H93.25 (Central auditory processing disorder) is on line 345 NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS

CPT 92620 Evaluation of central auditory function, with report; initial 60 minutes
CPT 92621 Evaluation of central auditory function, with report; each additional 15 minutes

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

Line 662

The following Interventions are prioritized on Line 662 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
92620-92621	Evaluation of central auditory function	Insufficient evidence of effectiveness	January 2005

Evidence:

1) **Moore 2011**, review on the diagnosis and management of auditory processing disorder
    a. Currently, APD is ill defined, and training-based interventions appear to have limited effectiveness
    b. Testing is confounded by issues of attention and memory
    c. I am unaware of any study that has examined the efficacy of auditory training for the management of APD without a concurrent diagnosis of speech and language difficulties, and that appeared to be true also for the 23 papers reviewed by Fey et al. (2011) in the clinical forum
2) **Fey 2011**, systematic review of auditory processing disorder interventions
    a. N=25 studies (121 subjects)
    b. The bases for diagnosis of APD in these studies generally was teacher concern for listening and related academic abilities or low overall performance on one or a battery of tests, usually including the Staggered Spondaic Word Test (SSW; Katz, Basil, & Smith, 1963), the SCAN-C Test for Auditory Processing Disorders in Children—Revised (Keith, 1999), and tests of speech in noise
    c. The interventions included “traditional listening” treatments, AIT, Fast ForWord, and Earobics
    d. Some support exists for the claim that auditory and language interventions can improve auditory functioning in children with APD and those with primary spoken language disorder. There is little indication, however, that observed improvements are due to the auditory features of these programs. Similarly, evidence supporting the effects of these programs on spoken and written language functioning is limited
    e. Conclusion: The evidence base is too small and weak to provide clear guidance to speech-language pathologists faced with treating children with diagnosed APD

Central Auditory Function Testing

Expert guidelines:

1) **Heine 2015**, systematic review of clinical practice guidelines for CAPD
    a. there is currently no universally accepted definition of CAP and CAPD and no consensus regarding assessment, diagnosis or treatment of this disorder.
    b. 6 guidelines identified
        i. American Academy of Audiology Clinical Practice Guidelines (see below); American Speech and Hearing Association (ASHA) (Central) Auditory Processing Disorders technical report; British Society of Audiology, Position Statement Auditory Processing Disorder (APD); Canadian guidelines on auditory processing disorder in children and adults: Assessment and Intervention; Colorado Department of Education, Auditory Processing Disorders: A team approach to screening, assessment & intervention practices; and the British Society of Audiology Practice Guidance
    c. Many guidelines do not reference the level of evidence supporting a recommendation
2) **Iliadou 2017**, European consensus on auditory processing disorder
    a. Auditory processing evaluation in the clinical setting is largely based on psychoacoustic test batteries of verbal and non-verbal stimuli and may be ancillary completed with electrophysiological or objective audiological measures, such as acoustic reflex thresholds, tympanometry, ABR (speech and noise ABR included), or OAEs (suppression included)
    b. The interventions should be as individualized as possible addressing (i) environmental modifications, (ii) use of FM systems, and (iii) systematic auditory training. Management needs to be multidisciplinary, and it is important that this is implemented in the educational environment for affected individuals who are still in education
3) **American Academy of Audiology 2010**, clinical practice guideline for the diagnosis, treatment and management of children and adults with central auditory processing disorder
    a. Expert taskforce developed
    b. Audiologists, related professionals, and clinical scientists generally agree that some of the tests for (C)APD in current clinical use lack rigorous psychometric design, construction, and validation. Populations “suspected” or “presumed” have (C)APD (e.g., those with learning disabilities, reading problems, or attention deficits) cannot be used to determine validity, efficiency, or clinical norms for diagnostic tests of central auditory processing. Similarly, speech-language, psychological, and other tests cannot be used to diagnose (C)APD, even if the term “auditory processing” is included in their titles or subtest descriptions.
    c. Efforts to develop new clinical measures of (C)APD and refine existing procedures must include systematic assessment of test performance and the implementation of accepted principles of psychometric test construction. Substantial evidence regarding test performance (e.g., reliability, validity, sensitivity, and specificity) is lacking for some of the commonly used tests of central auditory processing
    d. Historically, there has been considerable debate as to the appropriate “gold standard” for (C)APD and other disorders (e.g., language) in children
    e. . Given the complexity and redundancy of the central auditory system, accurate diagnosis typically requires the administration of more than one test; however, while sensitivity may be improved by increasing the number of tests in the battery, the administration of too many central auditory tests may compromise specificity

Central Auditory Function Testing

Other payer policies:

1) **Aetna 2023**
    a. Aetna considers any diagnostic tests or treatments for the management of auditory processing disorder (APD) (previously known as central auditory processing disorder (CAPD)) experimental and investigational because there is insufficient scientific evidence to support the validity of any diagnostic tests and the effectiveness of any treatment for APD.
2) **Excellus BCBS 2022**
    a. Based upon our criteria and assessment of the peer-reviewed literature, auditory processing disorder (APD) testing is considered not medically necessary, as it does not improve patient outcomes, and there is insufficient evidence to support the validity of the diagnostic tests utilized in diagnosing an auditory processing disorder

Public comment disposition

No public comments were received during the early packet public comment period.

Central Auditory Function Testing

HERC staff summary: Central auditory processing disorder is a vaguely defined condition with no consensus on diagnostic criteria. There is no universally accepted method of screening for CAPD. No pharmacologic agent has been demonstrated as effective specifically for CAPD. Behavioral and other interventions for CAPD have limited, if any, evidence of effectiveness. No private payer with an identifiable policy on CAPD covered testing or treatment for the condition.

HERC staff recommendations:

1) Make no change to the current placement of evaluation for central auditory function (CPT 92629 and 92621)
    a. Update the date of last review in GN173 as shown below
2) Delete ICD-10-CM H93.25 (Central auditory processing disorder) from line 345 NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS and add to line 655 NEUROLOGIC CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS
Line 662

The following Interventions are prioritized on Line 662 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**
92620-92621	Evaluation of central auditory function	Insufficient evidence of effectiveness	~~January 2005~~ November 2023

LSHSS

Review

The Diagnosis and Management of Auditory Processing Disorder

David R. Moore[a]

Purpose: To provide a personal perspective on auditory processing disorder (APD), with reference to the recent clinical forum on APD and the needs of clinical speech-language pathologists and audiologists.
Method: The Medical Research Council–Institute of Hearing Research (MRC-IHR) has been engaged in research into APD and auditory learning for 8 years. This commentary is informed by and describes that and other research.
Results: Currently, APD is ill defined, and training-based interventions appear to have limited effectiveness. However, there remains a huge clinical and caregiver appetite for evidence-based information about children's listening difficulties and how they might be managed. MRC-IHR research suggests that both the problem and the solution revolve around auditory cognition and, in particular, working memory and attention. Children who are poor listeners tend to have a range of cognitive difficulties. But, results of training studies within and beyond auditory science indicate that training primarily influences sustained attention (focus) rather than more basic sensory detection or discrimination.
Conclusion: Providing logical and rigorous scientific information on the nature and alleviation of listening difficulties in children should remain a high priority for speech, language, and hearing research. We should be optimistic that collaboration between clinicians and researchers will result in much greater understanding and improved management of listening disorders in the near future.

Key Words: auditory processing disorder, auditory learning, listening problems

It is very easy to criticize the notion of auditory processing disorder (APD). As discussed in several articles in the preceding clinical forum (Kamhi, 2011; Richard, 2011) and elsewhere (Jerger, 2009), thinking about APD has been pulled in one direction or another for more than 30 years. However, two views currently dominate thinking about APD, as promoted by the American Speech-Language-Hearing Association (ASHA) and other professional bodies. One is that APD is a neurological disorder and that studies of clients with known lesions of the central auditory nervous system (CANS) provide the theoretical and procedural underpinning (the "gold standard") of diagnosis and management. The second view is that APD can and should be understood by reference to basic auditory processing, to the known, bottom-up physiology and psychology of hearing in response to simple sounds such as tones and broadband noise. As I explain in the following paragraphs, I do not believe that either of these views is very helpful.

APD is a problem arising from clinical need and expediency. Clients, especially children, come to clinics because of listening difficulties. If they turn out not to have a hearing loss or a speech impairment, the question arises as to what to do with them. They could be, and are, referred to other clinics for further assessment. But, if the primary problem is auditory, as implied in the label APD, it becomes the job of the audiologist to test for it and to make recommendations for its management. However, our research (Moore, Ferguson, Edmondson-Jones, & Ratib, 2010; Moore, Cowan, Riley, Edmondson-Jones, & Ferguson, 2011), conducted on children drawn from the mainstream school population, and that of others (Dawes & Bishop, 2009; Watson & Kidd, 2009), suggests that poor listening is not primarily associated with poor *thresholds* on tests of basic auditory processing. Instead, we have found that poor listening is associated with *variable* performance on those tests. In short, our evidence suggests that most listening problems for children are due to poor attention or working memory. Whether those cognitive problems are specifically auditory or not is an important question for further research.

Two main strategies have been recommended for the management of APD. One involves environmental modification,

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LSHSS

Clinical Forum

Auditory Processing Disorder and Auditory/Language Interventions: An Evidence-Based Systematic Review

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Purpose: In this systematic review, the peer-reviewed literature on the efficacy of interventions for school-age children with auditory processing disorder (APD) is critically evaluated.
Method: Searches of 28 electronic databases yielded 25 studies for analysis. These studies were categorized by research phase (e.g., exploratory, efficacy) and ranked on a standard set of quality features related to methodology and reporting.
Results: Some support exists for the claim that auditory and language interventions can improve auditory functioning in children with APD and those with primary spoken language disorder. There is little indication, however, that observed improvements are due to the auditory features of these programs. Similarly, evidence supporting the effects of these programs on spoken and written language functioning is limited.
Conclusion: The evidence base is too small and weak to provide clear guidance to speech-language pathologists faced with treating children with diagnosed APD, but some cautious skepticism is warranted until the record of evidence is more complete. Clinicians who decide to use auditory interventions should be aware of the limitations in the evidence and take special care to monitor the spoken and written language status of their young clients.

Key Words: auditory processing disorder, auditory intervention, spoken language disorder, primary language disorder

As Richard (2011) indicated in her prologue to this clinical forum, there is a long, contentious history involving both the identification and treatment of children with auditory processing disorder (APD) by professionals in communication sciences and disorders. Despite this history of debate and disagreement, children with APD are regularly identified and treated by audiologists and speech-language pathologists (SLPs), and claims of success for treatments of many types abound. However, no systematic reviews of the treatment literature in this area have been published to date. The purpose of this systematic review is to examine and critically evaluate the literature on interventions that target the spoken and written language problems, as well as the possibly even more basic auditory processing problems, of children and youths with diagnosed APD.

Because of the disagreement that exists concerning the diagnosis of APD, we cast a broad net for our review by considering all treatment studies involving school-age children with diagnosed APD, regardless of the criteria used to make the diagnosis. Auditory interventions are often used to treat children with spoken language disorder who have not been diagnosed with APD. Therefore, we also included studies in which auditory interventions were used to address the spoken and written language abilities of children with primary language disorders.

There is no consensus in the field of speech-language pathology regarding criteria for distinguishing auditory interventions from language interventions, and many available

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Central Auditory Processing Disorder: a systematic search and evaluation of clinical practice guidelines

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clinical guidelines, evaluation, systematic reviews

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Abstract

Rationale, aims and objectives An increased interest in Central Auditory Processing Disorder has seen the publication of several guidelines to help inform clinical practice. The aim of this study was to conduct a systematic search and critically evaluate published guidelines to inform the ongoing development of evidence-based practice in this area.
Method A systematic search of the literature was conducted according to the Preferred Reporting Items for Systematic Reviews guidelines. Nominated guidelines were then critiqued using the Appraisal of Guidelines and Research and Evaluation (AGREE II) tool.
Results Five clinical practice guidelines in the area of Central Auditory Processing Disorder were identified. The British Society of Audiology guideline achieved the highest rating for scope and purpose, rigour of development and applicability and overall score.
Conclusions The AGREE II tool is an effective way to critically evaluate the quality of methodological reporting of clinical practice guidelines in the area of Central Auditory Processing Disorder and provides direction for the ongoing development of these guidelines in the future.

Acronyms and Abbreviations: Central Auditory Processing (CAP); Central Auditory Processing Disorder (CAPD); Clinical practice guideline (CPG); Preferred Reporting Items for Systematic Reviews (PRISMA); Appraisal of Guidelines and Research and Evaluation (AGREE II).

Introduction

Central Auditory Processing (CAP) and Central Auditory Processing Disorder (CAPD) have been described and debated in the literature over many years. However, there is currently no universally accepted definition of CAP and CAPD and no consensus regarding assessment, diagnosis or treatment of this disorder. This may be partly explained by the notion that it is a disorder that transgresses multiple professional disciplines including audiology, speech pathology and psychology.

One of the most quoted definitions of CAP and CAPD is by the American Speech and Hearing Association (ASHA) [1] who define CAP as 'the auditory mechanisms that underlie the following abilities or skills: sound localization and lateralization; auditory discrimination; auditory pattern recognition; temporal aspects of audition, including temporal integration, temporal discrimination (e.g. temporal gap detection), temporal ordering, and temporal masking; auditory performance in competing acoustic signals (including dichotic listening); and auditory performance with degraded acoustic signals' (p2). According to this definition, individuals with deficiency in any of these processes are clinically diagnosed as having CAPD [1].

CAPD may be apparent throughout the lifespan, however, it is of particular interest in the school-aged population since it is associated with language deficits, impaired literacy acquisition and generally poor academic performance [2–4]. The difficulty diagnosing CAPD is elucidated in a recent study by Dawes and Bishop [4] who investigated whether there was a difference in the learning profiles of children with CAPD ($n = 25$) and those with dyslexia ($n = 19$). Results of this study found that 52% of children with CAPD would also fit a diagnosis of dyslexia or specific language impairment or both.

The debate regarding CAPD goes beyond the issues related to diagnosis, and includes the use of terminology, differences in attribution of site-of-lesion, underlying mechanisms and co-morbidity [5]. This lack of consensus has been recently highlighted in the British Society of Audiology (BSA) 'white paper' [6]. In an attempt to provide guidance to clinicians, different professional bodies such as the American Academy of Audiology (AAA) [7], the Canadian Interorganizational steering group for speech

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A European Perspective on Auditory Processing Disorder-Current Knowledge and Future Research Focus

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Current notions of "hearing impairment," as reflected in clinical audiological practice, do not acknowledge the needs of individuals who have normal hearing pure tone sensitivity but who experience auditory processing difficulties in everyday life that are indexed by reduced performance in other more sophisticated audiometric tests such as speech audiometry in noise or complex non-speech sound perception. This disorder, defined as "Auditory Processing Disorder" (APD) or "Central Auditory Processing Disorder" is classified in the current tenth version of the International Classification of diseases as H93.25 and in the forthcoming beta eleventh version. APDs may have detrimental effects on the affected individual, with low esteem, anxiety, and depression, and symptoms may remain into adulthood. These disorders may interfere with learning *per se* and with communication, social, emotional, and academic-work aspects of life. The objective of the present paper is to define a baseline European APD consensus formulated by experienced clinicians and researchers in this specific field of human auditory science. A secondary aim is to identify issues that future research needs to address in order to further clarify the nature of APD and thus assist in optimum

diagnosis and evidence-based management. This European consensus presents the main symptoms, conditions, and specific medical history elements that should lead to auditory processing evaluation. Consensus on definition of the disorder, optimum diagnostic pathway, and appropriate management are highlighted alongside a perspective on future research focus.

Keywords: auditory processing disorder, auditory processing, hearing, listening difficulties, ear, central auditory nervous system, hidden hearing loss, psychoacoustic

INTRODUCTION

Hearing loss (HL), i.e., reduced pure tone sensitivity affects over 5% of the world's population (1) and is the fifth leading cause of Years Lived with Disability, a component of the Disability-Adjusted Life Year, used to measure the global burden of disease (2). This hearing impairment, however, does not include the children and adult individuals who have normal hearing sensitivity but who experience auditory processing difficulties in everyday life that are reflected in reduced performance in other audiometric tests such as speech in noise or complex non-speech sound perception (3). This disorder is defined as "Auditory Processing Disorder" (APD) or "Central Auditory Processing Disorder" (CAPD) and is currently classified in ICD-10 as H93.25 for both acquired and congenital forms.[1] It has been proposed that this disorder may be differentiated as (i) developmental APD, (ii) acquired APD (e.g., as a consequence of infections, neurologic trauma, stroke, or excessive noise exposure), and (iii) secondary APD (4). However, this categorization may be problematic in that it does not include presentations like "central presbycusis" (5) which may affect older adults with or without other cognitive impairments (6), or the distinct non-verbal processing disorders that are present in some but not all types of dementia (7, 8) of which few have a genetic component, or in neurological disorders with a genetic basis such as multiple sclerosis or in psychiatric disorders where auditory processing deficits are successfully addressed with auditory training (9). The ICD-11 Beta version includes APD under diseases of the ear following a proposal by two of the authors of this paper [Vasiliki (Vivian) Iliadou and Doris-Eva Bamiou] seconded/commented upon by other co-authors. The HL sequelae are well established, with higher rate of unemployment or employment at a lower grade of the hearing impaired (10) and increased risk for dementia (11), mental illness/depression (12, 13), and social isolation (14). APD may have similar detrimental effects on the affected individual, with low esteem/anxiety (15), anxiety, and depression (16) and symptoms in developmental APD, which may persist in adulthood (17). These may burden community inclusion while interfering with communicational, social, emotional, and academic-work aspects of life. Academic skills affected are mostly in higher-order language like reading and spelling (18). External factors contributing to negative psychosocial well-being in children with APD are environmentally based issues and support dissatisfaction (19).

Although APD is attracting increasing interest and recognition as a clinical entity among clinicians on the field and scientific organizations throughout the world [e.g., Ref. (4, 20–27)], there is ongoing debate regarding its diagnosis and management. Most of this debate is based on (i) rejecting currently used diagnostic Auditory processing test batteries even though they are the best available as a gold standard approach, (ii) reaching conclusions regarding APD based on research of APD suspected individuals who have a primary diagnosis of another developmental disorder, without explicitly testing for APD. As a consequence, there is limited availability of APD testing for the affected individuals both in Europe (28, 29) and beyond (30), while the expertise regarding APD within clinical audiological setups is variable.

The objective of the present paper is to define a baseline European APD consensus by experienced clinicians and researchers in this specific field of human auditory science. A second aim is to identify issues that future research needs to address in order to further clarify the nature of APD and thus assist in optimum diagnosis and evidence-based management. Authors of this position paper work in European countries and conduct both clinical and research work in the APD field. Five of the authors (Doris-Eva Bamiou, Martin Ptok, Vasiliki (Vivian) Iliadou, Christiane Kiese-Himmel, and Andreas Nickisch) of this position paper are at the top five publishing APD research while working exclusively in Europe according to the scopus database (United Kingdom, Germany, and Greece).

WHEN TO INITIATE APD DIAGNOSTIC

By the end of the nineteenth century, tuning forks and, some decades later, audiometric devices greatly helped to understand the extent and the site of lesion of HLs. Examinations focusing on pure tones thoroughly characterized and quantified threshold shifts which in most cases were congruent with impaired hearing of other acoustic signals in everyday life like spoken speech. However, clinical observations, especially in children and neurological adults, cast doubt that measurable threshold shifts could always explain the extent of reported hearing and listening impairment. Especially in cases with no threshold shift in pure tone audiometry but with hearing and listening difficulties, such incongruencies had to be explained. This finally

[1]Other countries in Europe may have different ways of coding, e.g., in Germany, APD must be coded as F80.20 to get reimbursement from insurance companies.

Abbreviations: ABR, Auditory Brainstem Responses; ANSD, Auditory Neuropathy Spectrum Disorder; APD, Auditory Processing Disorder; CAPD, Central Auditory Processing Disorder; HHL, Hidden Hearing Loss; HL, Hearing Loss; OAE, Otoacoustic Emissions; EEG, ElectroEncephaloGraphy; MEG, MagnetoEncephaloGraphy; fMRI, Functional Magnetic Resonance Imaging.

American Academy of Audiology

Clinical Practice Guidelines

Diagnosis, Treatment and Management of Children and Adults with Central Auditory Processing Disorder

August 2010

AMERICAN ACADEMY OF AUDIOLOGY
www.audiology.org

EXECUTIVE SUMMARY

The following clinical practice guidelines provide evidence-based recommendations for the diagnosis, treatment, and management of children and adults with (central) auditory processing disorder ([C])APD). The American Academy of Audiology (AAA) appointed a task force to develop a document to provide direction to clinicians involved in this practice area, as well as to provide a resource to the AAA and its membership for communication with the public. This document was to build on and expand prior statements and reports on (C)APD issued by other professional associations (e.g., ASHA, 2005b) and consensus panels (e.g., Jerger & Musiek, 2000). The present guidelines focus on four major areas of (C)APD: 1) patient history and selection criteria, 2) diagnosis, 3) intervention, and 4) professional issues, education, and training. The guidelines emphasize the following points and contain the following recommendations.

(C)APD is seen in a wide array of populations, including children and adults. It can be the result of a number of different etiologies that involve deficits in the function of the central auditory nervous system (CANS). Neurological involvement ranging from degenerative diseases to exposure to neurotoxic substances can result in (C)APD. In addition, developmental, communicative, and learning-related problems, as well as peripheral hearing loss and aging processes, can impact central auditory processing. A substantial number of individuals seen for (C)APD evaluations are children and adults with disorders of auditory processing due to diffuse central nervous system (CNS) dysfunction but with no identifiable lesions. These individuals often have difficulties with language, learning, and reading in addition to their auditory deficits. In questioning the patient or informant, it is essential that the clinician consider a range of issues, including hearing, medical, educational, social, developmental, and communicative status. A comprehensive history often reveals potential comorbid conditions that may affect test performance and the interpretation of the test results. It also ensures the selection of diagnostic tests most appropriate to the individual's profile and most likely to provide valid and reliable information leading to accurate diagnosis. Patient factors and considerations include: age, cognitive ability, general behavior, speech, language and hearing status, motivation, and attention issues. An in-depth, relevant history and careful test selection process will maximize the power of the diagnostic test battery.

The purposes of central auditory testing are two-fold: (1) to identify the presence of abnormalities in or dysfunction of the CANS and diagnose (C)APD, and (2)to describe the nature and extent of the disorder for purposes of developing management and intervention programs for affected individuals. Accurate diagnosis is dependent on the administration and interpretation of sensitive, efficient, and well-normed behavioral and electrophysiologic measures of central auditory function. Given the complexity and redundancy of the central auditory system, accurate diagnosis typically requires the administration of more than one test; however, while sensitivity may be improved by increasing the number of tests in the battery, the administration of too many central auditory tests may compromise specificity. The clinician should select normed tests that provide insights regarding the presence of (C)APD, assessment of various central auditory processes and behaviors, and evaluation of the integrity of the CANS at multiple sites and levels. Tests that have been shown to be sensitive and specific to known involvement of the CANS (e.g., through lesion studies, brain imaging, and other methods) provide guidance regarding the integrity of the various auditory processes and the CANS. Tests should be selected that have appropriate normative data. No matter how efficient a test may prove to be, it is of no clinical utility if appropriate norms are not available.

Intervention for (C)APD has received much attention recently due to advances in neuroscience demonstrating the key role of auditory plasticity in producing behavioral change through intensive training. With the documented potential of a variety of auditory training procedures to enhance auditory processes, the opportunity now exists to change the brain, and in turn, the individual's auditory behavior through a variety of multidisciplinary approaches that target specific auditory deficits. Customizing therapy to meet the client's profile (e.g., age, cognition, language, intellectual capacity, comorbid conditions) and functional deficits typically involves a combination of bottom-up and top-down approaches.

In addition to auditory training, the management of acoustic conditions (e.g., classroom acoustics) and signals (e.g., through high fidelity listening devices), coupled with educational, cognitive, language, metacognitive, and metalinguistic strategies can serve to reduce auditory deficits and lead to more effective listening, communication, and learning.

While there has been significant progress in professional education and training in (C)APD, as evidenced by the increasing number of conference presentations, published articles, and professional association reports on this topic, there remains a documented need for additional improvements in this area at the graduate education level and through continuing education. In particular, additional course work in the basic sciences will provide clinicians with the knowledge needed to critically apply diagnostic tools and treatment strategies.

Among the most pressing professional issues is the lack of intensive treatment provided in schools. Ironically, although large numbers of individuals with (C)APD are children in schools, current school policies and caseloads do not support the intensive training required for cortical reorganization and behavioral change. Because (C)APD is often a multifaceted problem, a team approach is needed to best serve the individual and his/her family. (C)APD must be diagnosed by an audiologist; however, other professionals can and should be involved in the broad assessment of the functional deficits experienced by the individual with (C)APD and in planning the intervention activities needed to minimize those deficits. Reimbursement is another pressing professional issue. Despite improved reimbursement rates for some diagnostic services, the rates remain inadequate, and clinicians cannot use some current procedural terminology (CPT) codes with certain third party payers (e.g., Medicare) to secure reimbursement for their intervention efforts. The AAA and other professional associations representing audiologists must continue their efforts to educate physicians, teachers, parents, and legislators and their staffers to the level of education, training, instrumentation, and clinical time needed for the accurate and early diagnosis and multidisciplinary assessment of (CAPD) and its intervention. The support and advocacy of these professional associations may lead to smaller caseloads and more therapy time per child in schools, as well as positive changes in reimbursement rates.

These guidelines are not exhaustive and are not intended to serve as the sole source of guidance for the clinician, nor are they intended to replace clinical judgment. Rather these guidelines reflect the best evidence-based practices in this area at this time as judged by the members of this task force. They should be used as a framework to guide the clinician in decision-making and best clinical practices as they relate to the diagnosis and treatment of (C)APD in various clinical populations presenting with this disorder.

INTRODUCTION

The following clinical practice guidelines for (central) auditory processing disorder [(C)APD] were developed by a task force appointed by the American Academy of Audiology (AAA). The nine-member task force included experts from various academic and clinical settings with extensive clinical and research experience and knowledge of (C)APD, representing varied philosophies and multiple perspectives. The document is written primarily for clinicians. However, the guidelines are not intended to be an exhaustive treatise on (C)APD, but rather to serve as a practical directive for those serving individuals with this disorder. Despite the strong research base underlying central auditory processing and its disorders, continued research is needed to improve our understanding of this disorder and the efficacy of the clinical services provided to individuals with (C)APD and their families. Although not the primary focus of this task force report, comments regarding research needs can be found at the end of each major section of these guidelines.

Included in this introduction is the definition of (C)APD that framed the task force's work, as well as definitions of related

Photoscreening 2023

Plain Language Summary:

Coverage question: Should OHP cover a test (photoscreening) that checks a child's vision using a special camera instead of an eye chart? It helps find out how well a child can see.

Should OHP cover this test?
Option 1: No. This test is not as cost-effective as using an eye chart for screening.
Option 2: Yes, cover this test because experts recommend it.

Coverage Question: Should coverage be added for instrument-based ocular screening for children?

Question source: Holly Jo Hodges, CCO medical director

Background: Photoscreening is a form of pediatric vision screening that uses a special-purpose camera to determine how well a child can see. It is an alternative to visual acuity-based screening with an eye chart. By detecting special light reflexes from each eye the devices produce images that can help identify refractive errors (like a prescription for glasses) and ocular misalignments (strabismus). When present, these conditions place a child at risk for amblyopia (lazy eye). Photoscreening is particularly useful with pre-verbal children (under age 3 yrs), young children (age 3-5 yrs) and older, non-cooperative or non-verbal children. As such, photoscreening offers an alternative to traditional visual acuity screening, providing earlier detection of potential vision problems than has been possible with traditional testing.

The USPSTF (2011) recommends vision screening for all children at least once between the ages of 3 and 5 years, to detect the presence of amblyopia or its risk factors (grade B recommendation). The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of vision screening for children <3 years of age (I statement). The USPSTF lists photoscreening as one option for vision screening. Per the USPSTF statement from 2017: "Various screening tests are used in primary care to identify vision abnormalities in children, including the red reflex test, the cover-uncover test, the corneal light reflex test, visual acuity tests (such as Snellen, LEA Symbols, and HOTV charts), autorefractors and photoscreeners, and stereoacuity tests."

Previous HSC/HERC reviews:

Photoscreening was reviewed in 2015. An older USPSTF report (Chou 2011) and older AAP guideline (2012) were reviewed at that time. The staff conclusion was "Early vision screening is recommended by major evidence based organizations; however, clinical exam and standard eye chart testing appears to be sufficient. Photoscreening and similar technology needs to be further studied before widespread implementation." Photoscreening was excluded for coverage.

Photoscreening was again discussed in 2019. During that review, the 2017 USPSTF report and the 2016 AAP guidelines were reviewed. The AAP guideline listed instrument-based screening as listed as one option "when available" with other options being physical exam and standard of care being eye chart testing. Based on these recommendations, photoscreening was placed on line 502, as more expensive than other equally effective tests.

Photoscreening 2023

Current Prioritized List/Coverage status:

CPT 99174 Instrument-based ocular screening (eg, photoscreening, automated-refraction), bilateral; with remote analysis and report
CPT 99177 (Instrument based ocular screening (eg, photoscreening, automated-fractions),bilateral; with onsite analysis)

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

Line 502

The following interventions are prioritized on Line 502 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS:

Procedure Code	Intervention Description	Rationale	Last Review
99174, 99177	Photoscreening	More costly than equally effective methods of screening	May 2019

Evidence:

1) **Horwood 2021,** systematic review on photoscreening cost-effectiveness
    a. N=60 papers
    b. Only 13% of studies reported actual amblyopia detection as an outcome
    c. Reporting of follow up rates and long-term outcomes were poor or absent
    d. PPVs even for risk factors, not actual amblyopia or reduced vision, varied widely from 19% to >80%, but were generally lowest in the youngest children. Referral rates were particularly high in very young children e.g. 19% at 6–9 months, 20% at 9–36 months, 16% at < 12 months, but often did not result in immediate treatment. One study reported that only 11% of 123 children under 36 months referred received any intervention, compared to a 74% in children over 36 months
    e. Photoscreening is being widely adopted, and in many different ways, but with poor availability of local, regional or national protocols, audit or monitoring of long-term outcomes or costs. There is weak evidence of optimum timing, frequency, or referral criteria to maximize outcomes whilst minimizing monetary and societal costs. Despite published guidelines there is still no clear evidence what level of refractive error constitutes an amblyopia risk-factor at different ages, or the optimum time to treat risk factors
    f. Evidence that photoscreening reduces amblyopia or strabismus prevalence or improves overall outcomes is weak, as is evidence of cost-effectiveness, compared to later visual acuity (VA) screening. Currently, the most cost-effective option seems to be a later, expert VA screening with the opportunity for a re-test before referral.
2) **Jonas 2017**, Evidence review for the USPSTF report on vision screening
    a. 11 studies reported on photoscreeners (6 studies on MTI photoscreener, 2 on iScreen, 2 on Visiscreen, 2 on Otago Photoscreener, 1 on off-axis-type photoscreener)

   i. Sensitivity for amblyopia ranged from 0.37-0.95
   ii. Specificity for amblyopia ranged from 0.89-1.0
b. Eleven fair-quality studies (6187 observations; n = 63-3121) assessed photoscreeners. Generally, most studies reported moderate positive likelihood ratios and small negative likelihood ratios. Many of the studies evaluating photoscreeners enrolled children younger than 3 y

Expert guidelines:

1) **American Academy of Ophthalmology and the American Association for Pediatric Ophthalmology and Strabismus 2022,** Joint policy statement on vision screening for infants and children
   a. Photoscreening and handheld autorefraction may be electively performed in children 12 months to 3 years of age, allowing earlier detection of conditions that may lead to amblyopia. Photoscreening and handheld automated refraction are recommended as an alternative to visual acuity screening with vision charts (typically used for children 3 through 5 years of age) and in children who are unable or unwilling to cooperate with routine acuity screening with vision charts (but are not superior to vision chart testing for children able to participate). The use of vision charts to assess amblyopia in children 3 to 5 years of age remains a viable practice at the present time.
2) **Donohue 2016**, Committee on Practice and Ambulatory Medicine, American Academy of Pediatrics; Section on Ophthalmology, American Academy of Pediatrics; American Association of Certified Orthoptists; American Association for Pediatric Ophthalmology and Strabismus; American Academy of Ophthalmology. Procedures for the evaluation of the visual system by pediatricians
   a. If available, instrument-based screening can be attempted beginning at age 12 months,11 and a previous study has demonstrated better eventual outcomes for children undergoing their first photoscreening before 2 years of age
   b. Once children can read an eye chart easily, optotype-based acuity should supplement instrument-based testing. The actual age for this is not yet well established and likely varies depending on the child
   c. Photoscreening has been shown to have high sensitivity and specificity in community and office settings.
3) **USPSTF 2017**, Vision Screening in Children Aged 6 Months to 5 Years US Preventive Services Task Force Recommendation Statement
   a. The USPSTF recommends vision screening at least once in all children aged 3 to 5 years to detect amblyopia or its risk factors. (B recommendation) The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of vision screening in children younger than 3 years. (I statement)
   b. Screening tests listed: Various screening tests are used in primary care to identify vision abnormalities in children, including the red reflex test, the cover-uncover test, the corneal light reflex test, visual acuity tests (such as Snellen, LEA Symbols, and HOTV charts), autorefractors and photoscreeners, and stereoacuity tests.

Other payer policies:

Aetna and Cigna both consider photoscreening to be required as a USPSTF level B recommendation

Photoscreening 2023

Expert input:

Lorri Wilson, OHSU pediatric ophthalmology

> I think one important piece of information to consider is eye chart vision screens are not possible (or very difficult) to obtain accurately in children less than 5 (certainly less than 3 years old) or older nonverbal/noncooperative children, but earlier diagnosis and treatment of amblyopia leads to better outcomes.

Leah Reznick, OHSU pediatric ophthalmology

> Anecdotally, the photoscreening has made a huge difference in early detection of amblyopia and strabismus. From being in practice before and after the incorporation of photo-screeners, children from my referring practices who have photoscreening have significantly better visual outcomes (earlier detection of significantly decreased vision, cataracts, and ocular misalignment).

Public comment disposition

No public comments were received during the early packet public comment period.

Photoscreening 2023

HERC staff summary:

Photoscreening is recommended as one option for visual acuity testing in the USPTSF, AAP, and ophthalmology society guidelines. The AAP recommends photoscreening, when available, for screening younger children and visual acuity testing for screening older children. The evidence for the effectiveness of photoscreening for detection of amblyopia or for impacting treatment outcomes is very weak. The AAP guidelines recommend photoscreeners as the test of choice for younger children (younger than age 3); however, vision screening for children under age 3 is a USPSTF "I" recommendation. Ophthalmology society joint recommendations state that "Photoscreening and handheld automated refraction are recommended as an alternative to visual acuity screening with vision charts (typically used for children 3 through 5 years of age) and in children who are unable or unwilling to cooperate with routine acuity screening with vision charts (but are not superior to vision chart testing for children able to participate)." Most private payers consider photoscreening to be required under the USPSTF level B recommendation for visual screening in children under the age of 5.

HERC staff recommendation:

1) Option 1: continue lack of coverage of photoscreening as a less cost-effective option for visual screening and most appropriate for children under age 3, a group not included in the USPSTF "B" recommendation for visual screening
    a. Update the date of last review in GN172

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

Line 502

The following interventions are prioritized on Line 502 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS:

Procedure Code	Intervention Description	Rationale	Last Review
99174, 99177	Photoscreening	More costly than equally effective methods of screening	~~May 2019~~ November 2023

2) Option 2: add coverage for photoscreening due to expert recommendation
    a. Add photoscreening CPT codes to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS and remove from line 502 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS
        i. CPT 99174 Instrument-based ocular screening (eg, photoscreening, automated-refraction), bilateral; with remote analysis and report
        ii. CPT 99177 (Instrument based ocular screening (eg, photoscreening, automated-fractions),bilateral; with onsite analysis)
    b. Remove the entry for photoscreening from GN172

Photoscreening 2023

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

Line 502

The following interventions are prioritized on Line 502 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS:

Procedure Code	Intervention Description	Rationale	Last Review
~~99174, 99177~~	~~Photoscreening~~	~~More costly than equally effective methods of screening~~	~~May 2019~~

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The ROYAL COLLEGE of OPHTHALMOLOGISTS

REVIEW ARTICLE

Scope and costs of autorefraction and photoscreening for childhood amblyopia—a systematic narrative review in relation to the EUSCREEN project data

Anna M. Horwood[1,2] · Helen J. Griffiths[3] · Jill Carlton[3] · Paolo Mazzone[3] · Arinder Channa[2] · Mandy Nordmann[4] · Huibert J. Simonsz[4] · on behalf of The EUSCREEN Foundation

Received: 4 December 2019 / Revised: 26 September 2020 / Accepted: 27 October 2020 / Published online: 30 November 2020

Abstract

Background Amblyopia screening can target reduced visual acuity (VA), its refractive risk factors, or both. VA testing is imprecise under 4 years of age, so automated risk-factor photoscreening appears an attractive option. This review considers photoscreening used in community services, focusing on costs, cost-effectiveness and scope of use, compared with EUSCREEN project Country Reports describing how photo- and automated screening is used internationally.

Methods A systematic narrative review was carried out of all English language photoscreening literature to September 10th 2018, using publicly available search terms. Where costs were considered, a CASP economic evaluation checklist was used to assess data quality.

Results Of 370 abstracts reviewed, 55 reported large-scale community photoscreening projects. Five addressed cost-effectiveness specifically, without original data. Photoscreening was a stand-alone, single, test event in 71% of projects. In contrast, 25 of 45 EUSCREEN Country Reports showed that if adopted, photoscreening often supplements other tests in established programmes and is rarely used as a stand-alone test. Reported costs varied widely and evidence of cost-effectiveness was sparse in the literature, or in international practice. Only eight (13%) papers compared the diagnostic accuracy or cost-effectiveness of photoscreening and VA testing, and when they did, cost-effectiveness of photoscreening compared unfavourably.

Discussion Evidence that photoscreening reduces amblyopia or strabismus prevalence or improves overall outcomes is weak, as is evidence of cost-effectiveness, compared to later VA screening. Currently, the most cost-effective option seems to be a later, expert VA screening with the opportunity for a re-test before referral.

Introduction

Amblyopia is usually asymptomatic and treatment is much more effective if carried out before the age of about 7 years [1–3], so it fulfils many of the World Health Organisation (WHO) criteria [4] as a target condition for screening. Unscreened prevalence is ~3% [5–7] in Caucasian populations, while that of significant refractive error can be up to 16% [7, 8] because many children with refractive errors will have normal best-corrected visual acuity (VA). Screening of young children significantly reduces amblyopia prevalence [5, 9] so it is recommended or mandated in many countries.

The US Preventative Services Taskforce [10] recommends vision screening at least once in children aged 3–5 years to detect amblyopia or its risk factors, but did not find sufficient evidence to determine the optimal screening interval in these children or to recommend screening under the age of 3 years [11].

It is still unclear how children should be screened to achieve optimal visual outcomes while avoiding excessive costs, false referrals, and unnecessary (or unnecessarily

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JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Vision Screening in Children Aged 6 Months to 5 Years
Evidence Report and Systematic Review for the US Preventive Services Task Force

Daniel E. Jonas, MD, MPH; Halle R. Amick, MSPH; Ina F. Wallace, PhD; Cynthia Feltner, MD, MPH; Emily B. Vander Schaaf, MD, MPH; Callie L. Brown, MD, MPH; Claire Baker

IMPORTANCE Preschool vision screening could allow detection and treatment of vision abnormalities during a critical developmental stage, preserving function and quality of life.

OBJECTIVE To review the evidence on screening for and treatment of amblyopia, its risk factors, and refractive error in children aged 6 months to 5 years to inform the US Preventive Services Task Force.

DATA SOURCES MEDLINE, Cochrane Library, CINAHL, and trial registries through June 2016; references; and experts, with surveillance of the literature through June 7, 2017.

STUDY SELECTION English-language randomized clinical trials (RCTs) or prospective cohort studies that evaluated screening, studies evaluating test accuracy, RCTs of treatment vs inactive controls, and cohort studies or case-control studies assessing harms.

DATA EXTRACTION AND SYNTHESIS Dual review of abstracts, full-text articles, and study quality; qualitative synthesis of findings. Studies were not quantitatively pooled because of clinical and methodological heterogeneity.

MAIN OUTCOMES AND MEASURES Visual acuity, amblyopia, school performance, functioning, quality of life, test accuracy, testability, and harms.

RESULTS Forty studies were included (N = 34 709); 34 evaluated test accuracy. No RCTs compared screening with no screening, and no studies evaluated school performance, function, or quality of life. Studies directly assessing earlier or more intensive screening were limited by high attrition. Positive likelihood ratios were between 5 and 10 for amblyopia risk factors or nonamblyogenic refractive error in most studies of test accuracy and were greater than 10 in most studies evaluating combinations of clinical tests. Inability to cooperate may limit use of some tests in children younger than 3 years. Studies with low prevalence (<10%) of vision abnormalities showed high false-positive rates (usually >75%). Among children with amblyopia risk factors (eg, strabismus or anisometropia), patching improved visual acuity of the amblyopic eye by a mean of less than 1 line on a standard chart after 5 to 12 weeks for children pretreated with glasses (2 RCTs, 240 participants); more children treated with patching than with no patching experienced improvement of at least 2 lines (45% vs 21%; $P = .003$; 1 RCT, 180 participants). Patching plus glasses improved visual acuity by about 1 line after 1 year (0.11 logMAR [95% CI, 0.05-0.17]) for children not pretreated with glasses (1 RCT, 177 participants). Glasses alone improved visual acuity by less than 1 line after 1 year (0.08 logMAR [95% CI, 0.02-0.15], 1 RCT, 177 participants).

CONCLUSIONS AND RELEVANCE Studies directly evaluating the effectiveness of screening were limited and do not establish whether vision screening in preschool children is better than no screening. Indirect evidence supports the utility of multiple screening tests for identifying preschool children at higher risk for vision problems and the effectiveness of some treatments for improving visual acuity outcomes.

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Related article page 836 and JAMA Patient Page page 878

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AMERICAN ACADEMY OF OPHTHALMOLOGY®

JOINT POLICY STATEMENT

Vision Screening for Infants and Children

A joint statement of the American Association for Pediatric Ophthalmology and Strabismus and the American Academy of Ophthalmology

Policy

The American Academy of Ophthalmology (Academy) and the American Association for Pediatric Ophthalmology and Strabismus (AAPOS) recommend timely screening for the early detection and treatment of eye and vision problems in America's children. This includes the institution of periodic vision screening during the preschool years. The US Preventive Services Task Force (USPSTF) recommends vision screening for children ages 3 to 5 years of age for the purpose of detecting amblyopia or risk factors for amblyopia.[1] Early detection of treatable eye disease in infancy and childhood can have far-reaching implications for vision and, in some cases, for general health.

Background

Good vision is essential for proper physical development and educational progress in growing children. The visual system of the young child is not fully mature. Equal input from both eyes is required for proper development of the visual centers in the brain. If a growing child's eye does not provide a clear, focused image to the developing brain, irreversible loss of vision in one or both eyes may result.

Early detection provides the best opportunity for effective treatment. The American Association for Pediatric Ophthalmology and Strabismus, the American Academy of Ophthalmology, the American Academy of Pediatrics, the American Academy of Family Physicians, and the American Association of Certified Orthoptists all recommend early vision screening.

Vision screening programs, administered by primary care providers, community programs, and schools should provide effective testing of preschool and early school-age children, which is done quickly, accurately, and with minimum expense. Effective vision screening maximizes the rate of

problem detection while minimizing unnecessary referrals and cost. Common eye conditions that can be detected include reduced vision in one or both eyes from amblyopia, uncorrected refractive errors, misalignment of the eyes (strabismus), or other eye defects.

Amblyopia is poor vision in an otherwise normal appearing eye that occurs when the brain does not fully recognize the sight from that eye. Two common causes are strabismus and a difference in the refractive error (need for glasses) between the two eyes. Treatment becomes less effective with age. If untreated, amblyopia can cause irreversible visual loss.

Strabismus is misalignment of the eyes in any direction. Amblyopia may develop when the eyes do not align. If early detection of amblyopia secondary to strabismus is followed by effective treatment, excellent vision may be restored. The eyes can be aligned in some cases with glasses and in others, with surgery. However, restoration of good alignment does not ensure elimination of amblyopia.

Refractive errors cause decreased vision, visual discomfort (eye strain), strabismus and/or amblyopia. The most common form is nearsightedness (poor distance vision). It is usually seen in school-age children and is treated effectively, in most cases, with glasses. While mild to moderate farsightedness is normal in preschool children and usually does not require glasses, high or asymmetric amounts of farsightedness can cause decreased vision, amblyopia, and strabismus unless treated with glasses. Astigmatism (imperfect curvature of the front surfaces of the eye) also requires corrective lenses if it produces blurred vision or discomfort. Uncorrected refractive errors can cause amblyopia, particularly if they are severe or are different between the two eyes.

The Academy and AAPOS have identified myopia as a high-priority cause of visual impairment. Interventions for delaying the onset of myopia and reducing myopia progression in childhood are available. Thus, periodic screening of children and evaluation of children at risk for myopia progression would allow for a targeted strategy to address myopia, as well as other ocular conditions.

In addition to detecting vision problems, effective screening programs should also emphasize a mechanism to inform parents of screening results and attempt to ensure that proper follow-up care, when necessary, is received.

Recommendations for community and school screening programs:

In the setting of community and school-based screening programs, screeners should have specific training in vision screening techniques and protocols as recommended by the Academy, and AAPOS. Children who do not pass these screenings should be referred for an additional ocular assessment performed by the primary care provider or an eye care provider with training and experience in treating children.

Recommendations for primary care:

In the primary care setting, the Academy and AAPOS recommend that an ocular assessment be performed whenever questions arise about the health of the visual system of a child of any age. In addition, even in the absence of specific signs or symptoms, they recommend that infants and children be routinely screened for vision problems as follows and that any child who does not pass one of more of these screening tests have an ophthalmological examination.

1. A pediatrician, family physician, or other properly trained health care provider should examine a newborn's eyes for general eye health and perform a red reflex test in the newborn nursery. Any baby with an abnormal red reflex requires urgent consultation. An ophthalmologist should be asked to examine all high-risk infants (i.e., those at risk of developing retinopathy of prematurity (ROP); those with a family history of retinoblastoma, glaucoma, or cataracts in childhood; those with a family history of retinal dystrophy/degeneration; those with systemic diseases or neurodevelopmental delays associated with eye problems; those with any opacity of the ocular media; or those with nystagmus).

2. From 1 month to 4 years of age, infants and toddlers should have their ocular health assessed at each routine well-child visit, including an external inspection, pupillary examination, corneal light reflection and assessment of fixation and following behavior. This assessment should address any concerns raised by the family or noted by the primary care provider.

3. Emphasis should be placed on checking visual acuity as soon as a child is cooperative enough to complete the assessment. Generally, this occurs between ages 3 ½ and 4 years. This assessment can be performed by a pediatrician, family practitioner, ophthalmologist, optometrist, orthoptist, nurse, or other appropriately trained individual. Screeners should not have a vested interest in the screening outcome. A child who is referred from a vision screening or is uncooperative at a second attempt at vision testing should be referred for a comprehensive eye evaluation. It is essential that a formal testing of visual acuity be performed by the age of 5 years.

4. Photoscreening and handheld autorefraction may be electively performed in children 12 months to 3 years of age, allowing earlier detection of conditions that may lead to amblyopia. Photoscreening and handheld automated refraction are recommended as an alternative to visual acuity screening with vision charts (typically used for children 3 through 5 years of age) and in children who are unable or unwilling to cooperate with routine acuity screening with vision charts (but are not superior to vision chart testing for children able to participate). The use of vision charts to assess amblyopia in children 3 to 5 years of age remains a viable practice at the present time.

5. Additional screening on each child should be done at routine school checks or well-child visits every 1-2 years after age 5 years. Routine comprehensive professional eye examinations performed on normal asymptomatic children have no proven medical benefit.

6. Children with possible or diagnosed learning disabilities, such as dyslexia, should undergo a comprehensive eye examination so that any undiagnosed vision impairment can be identified and treated. Such children should be referred for appropriate medical, psychological, and educational evaluations and treatment of any learning disability. There is inadequate scientific evidence to suggest that “defective eye teaming” and “accommodative disorders” are common causes of educational impairment.[2,3] Hence, routine screening for these conditions is not recommended.

Many serious ocular conditions are treatable if identified through screening during the preschool and early school-aged years. Many of these conditions are associated with a positive family history. Therefore, additional emphasis should be directed to screening high-risk infants and children, and, when necessary, screeners should readily refer such children to an ophthalmologist for a comprehensive eye evaluation.

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CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

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Procedures for the Evaluation of the Visual System by Pediatricians

Sean P. Donahue, MD, PhD, FAAP, Cynthia N Baker, MD, FAAP, COMMITTEE ON PRACTICE AND AMBULATORY MEDICINE, SECTION ON OPHTHALMOLOGY, AMERICAN ASSOCIATION OF CERTIFIED ORTHOPTISTS, AMERICAN ASSOCIATION FOR PEDIATRIC OPHTHALMOLOGY AND STRABISMUS, AMERICAN ACADEMY OF OPHTHALMOLOGY

abstract

Vision screening is crucial for the detection of visual and systemic disorders. It should begin in the newborn nursery and continue throughout childhood. This clinical report provides details regarding methods for pediatricians to use for screening.

This clinical report supplements the combined policy statement from the American Academy of Pediatrics (AAP), American Association for Pediatric Ophthalmology and Strabismus, American Academy of Ophthalmology, and American Association of Certified Orthoptists titled "Visual System Assessment in Infants, Children, and Young Adults by Pediatricians."[1] The clinical report and accompanying policy statement supplant the 2012 policy statement "Instrument-Based Pediatric Vision Screening,"[2] the 2003 policy statement "Eye Examination in Infants, Children, and Young Adults by Pediatricians,"[3] and the 2008 AAP policy statement "Red Reflex Examination in Neonates Infants and Children."[4] The policy statement articulates the screening criteria and screening methods, and the clinical report explains the various evaluation procedures that are available for use by the pediatrician or primary care physician.

VISUAL SYSTEM HISTORY ASSESSMENT

Relevant family history regarding eye disorders (cataracts, strabismus, amblyopia, and refractive error), eye surgery, and the use of glasses during childhood in parents or siblings should be explored. Parents' observations are also valuable in the history and review of systems. Questions that can be asked include:

1. Do your child's eyes appear unusual?
2. Does your child seem to see well?
3. Does your child exhibit difficulty with near or distance vision?
4. Do your child's eyes appear straight or do they seem to cross?
5. Do your child's eyelids droop or does one eyelid tend to close?
6. Has your child ever had an eye injury?

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OCULAR EXAMINATION

The ocular examination consists of the external examination, pupil examination, red reflex testing to assess ocular media, the examination of the ocular fundus by using ophthalmoscopy, and an assessment of visual function.

EXTERNAL EXAMINATION (LIDS/ORBIT/ CONJUNCTIVA/CORNEA/IRIS)

External examination of the ocular structures consists of a penlight evaluation of the eyelids, conjunctiva, sclera, cornea, and iris. Detection of abnormalities, such as ptosis, nonresolving conjunctivitis, or the presence of cloudy or enlarged corneas and/or photophobia, necessitates timely referral to an eye care specialist appropriately trained to treat children. Nasolacrimal duct obstruction that has not resolved by 1 year of age also should lead to referral. Thyroid disease can manifest by increased visibility of the superior cornea caused by eyelid retraction.

RED REFLEX TESTING

Red reflexes from the retinas can be used by the physician to great advantage. The red reflex test, or Bruckner test if performed binocularly, is used to detect opacities in the visual axis, such as a cataract or corneal abnormality, as well as abnormalities in the posterior segment, such as retinoblastoma or retinal detachment. The examiner also may detect subtle differences in the red reflex between the eyes, consistent with the presence of strabismus or refractive errors. The inequality of the red reflection or the interference with the red reflection can be noted in various conditions (Fig 1).

Red reflex testing should be performed in a darkened room (to maximize pupil dilation). Eye drops to further dilate the pupils are not necessary. The direct ophthalmoscope is set on "0," and while viewing

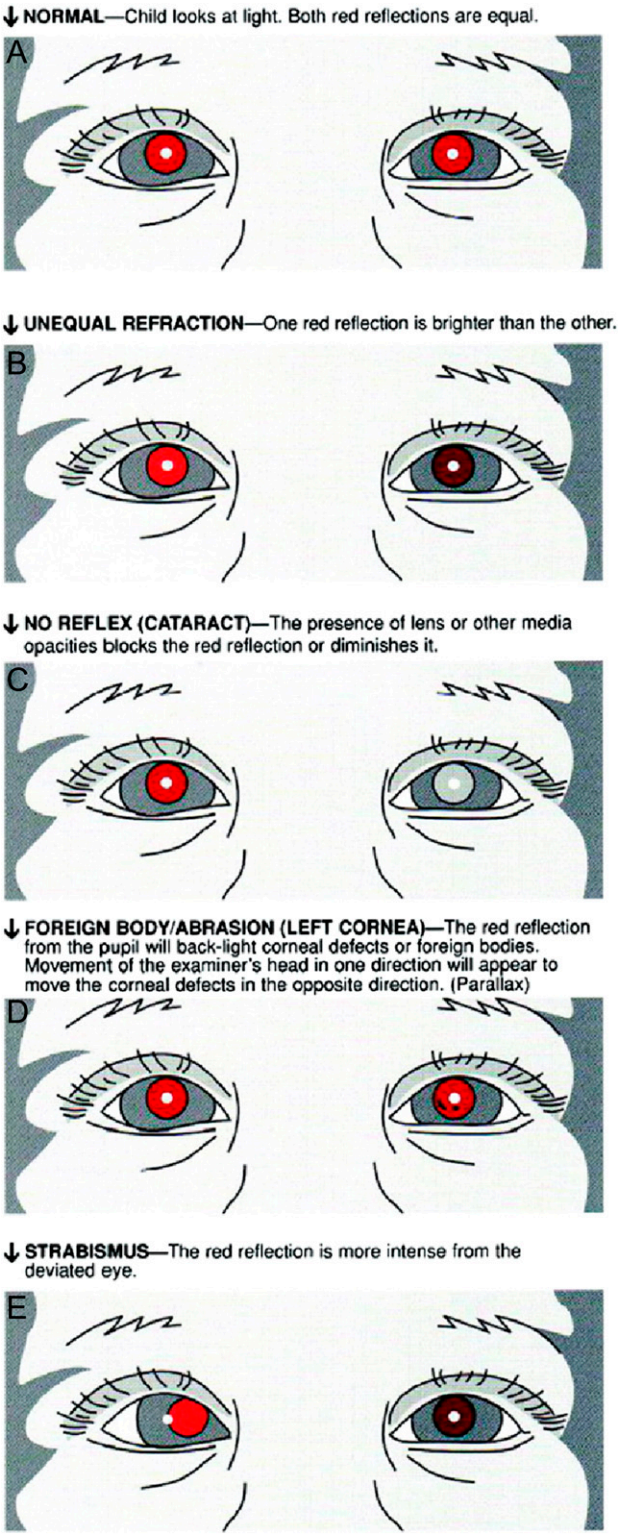

FIGURE 1

Red reflex examination. A, **NORMAL:** Child looks at light. Both red reflections are equal. B, **UNEQUAL REFRACTION:** One red reflection is brighter than the other. C, **NO REFLEX (CATARACT):** The presence of lens or other media opacities blocks the red reflection or diminishes it. D, **FOREIGN BODY/ ABRASION (LEFT CORNEA):** The red reflection from the pupil will back-light corneal defects or foreign bodies. Movement of the examiner's head in one direction will appear to move the corneal defects in the opposite direction. E, **STRABISMUS:** The corneal light reflex is temporally displaced in the misaligned right eye, indicating esotropia. (Used with permission of Alfred G. Smith, MD, ©1991.)

through it at a distance of approximately arm's length from the child, both pupils are evaluated simultaneously as the child looks at the light. To view more detail, the examiner can move closer to the child to assess each eye individually. The observed red reflexes can be compared and should be a light orange-yellow in color in lightly pigmented eyes or a dark red in darkly pigmented brown eyes. If normal, the 2 red reflexes should be identical in color, brightness, and size. A bright white or yellow reflex or, conversely, a dull or absent red reflex can be an indication of a significant abnormality that necessitates further evaluation by a pediatric ophthalmologist, or if unavailable, a comprehensive ophthalmologist or optometrist with specialized interest in the treatment of children, and who uses cycloplegia (dilating drops) as part of his or her routine evaluation. Because there is often considerable variation in the qualitative nature of the red reflex among patients without eye abnormalities, the frequent, routine assessment of the red reflex will help the primary care physician better distinguish an abnormality of the reflex from a normal one.

PUPIL EXAMINATION

Both pupils should be equal, round, and equally reactive when light is directed toward either eye. Asymmetric responses to light may indicate visual system dysfunction. Moreover, asymmetry of pupil shape or difference in diameter greater than 1 mm can often be attributable to an ocular injury or disease or to a neurologic disorder. Differences in pupil size less than 1 mm can occur normally and are generally benign unless associated with ptosis or an ocular motility deficit.

OCULAR ALIGNMENT AND MOTILITY ASSESSMENT

The assessment of ocular alignment in the preschool- and early school-aged child is also important. The development of strabismus in children may occur at any age and, although often isolated, may also represent serious orbital, intraocular, or intracranial disease.

The corneal light reflex test and the cover test are each useful in identifying the presence of strabismus as well as in differentiating true strabismus from pseudostrabismus.

The corneal light reflex test (ie, Hirschberg test) is performed with a penlight directed onto the child's face from arm's length away and by observing the symmetrical location of the white pinpoint light reflexes while the child gazes at the light. Normally, these reflexes fall symmetrically in or near the center of the pupils. An abnormal response occurs when the reflex in one eye is centered in the pupil while the reflex in the opposite eye is displaced nasally, temporally, or vertically away from the pupil center (Fig 1). This asymmetry of the reflexes typically indicates the presence of strabismus.

The cover test should be performed while the child fixates on a small, interesting target, such as a small toy or sticker on a tongue depressor. The bright beam of a penlight does not provide a comfortable target and does not adequately stimulate accommodation (focusing). As the child attends to the target, each eye is alternately covered. A shift in an eye's alignment as it assumes fixation onto the target is a possible indication of strabismus.

Strabismus in the neonatal period is not unusual, and intermittent strabismus is often a normal finding in early infancy. However, constant horizontal strabismus that persists after 4 months of age does not resolve spontaneously.[5] Thus, any child older than 4 months with strabismus should be referred for evaluation.

Pseudostrabismus is the appearance of crossed eyes (esotropia) attributable to the presence of prominent epicanthal skin folds that cover the medial portion of the sclera on 1 or both eyes, giving the false impression of esotropia. The inability to differentiate strabismus from pseudostrabismus also necessitates referral.

Finally, the presence of unusual eye movements in an infant or young child may indicate nystagmus or a similar disorder and often indicates decreased vision or neurologic dysfunction. Nystagmus does not resolve spontaneously and often indicates afferent visual system dysfunction or neurologic disease and necessitates further evaluation by either an ophthalmologist or neurologist.

OPHTHALMOSCOPY

Use of the direct ophthalmoscope in older, cooperative children serves to visualize structures in the back of the eye, such as the optic nerve, retinal blood vessels, and central retina (fovea). To properly visualize these structures, the child looks into the distance at a target of interest. The ophthalmoscope is dialed to a +10 lens and the examiner focuses on the pupil from ~3 inches away. The examiner then gradually moves as close to the eye as possible while sequentially dialing less lens power until retinal vessels come into focus. These vessels can be followed to identify and view the optic nerve. The normal optic nerve has a yellow-pink color and is generally flat. To view the foveal reflex, the child is asked to look directly at the light of the ophthalmoscope. The normal foveal reflex should appear bright and sharp. Retinal hemorrhages can be observed after a normal vaginal delivery but are also the harbinger of severe child abuse; a swollen optic nerve may be an indicator of increased intracranial pressure.

ASSESSMENT OF VISUAL ACUITY IN PREVERBAL CHILDREN

The assessment of visual function in this very young age group is best

accomplished by evaluating the child's ability to fixate on and follow an object held before the child. A standard assessment strategy is to determine whether each eye can independently fixate on the object, maintain fixation on it for a short period of time, and then follow it as it is moved in various directions. The child should be awake and alert for this testing, and the targeted object should be a toy or something of interest to the child. Disinterest or poor cooperation can mimic a poor vision response. This assessment should first be performed binocularly and then repeated with each eye alternately covered. If poor binocular fixation and following behavior is noted after 3 months of age, an ocular or neurologic abnormality may be present. Similarly, asymmetry in responses between the 2 eyes in children of any age necessitates further evaluation.

ASSESSMENT OF VISUAL ACUITY IN OLDER CHILDREN

Children who are old enough to delineate objects on a wall-mounted or handheld eye chart can provide a direct measurement of visual acuity. For some children, this may be accomplished as young as 3 years, but for the typical healthy child, an accurate visual acuity can be achieved with a high degree of success at 4 years and older. Eyes should be tested monocularly, ensuring that the child does not peek with the fellow eye.

With traditional visual acuity screening, the selection of age-appropriate shapes or letters and specific testing methods is crucial in obtaining the most accurate screening results. Many children can identify optotypes (figures or a selection of distinct letters formatted on chart lines or presented singly on individual cards) by 4 years of age. Eye charts using lines of optotypes or matching cards with lines (crowding bars) around each optotype provide the most accurate assessments of visual acuity (Fig 2). Using cards with single optotypes but without crowding bars can overestimate visual acuity. Crowding bars surround an optotype and make individual letters more difficult to recognize by an amblyopic eye, thus increasing the sensitivity to detect amblyopia (Fig 2). Accurate assessment of visual acuity, therefore, is best accomplished by using a line of symbols or symbols with crowding bars around them.

The currently preferred optotypes are the LEA or HOTV symbols, although other new picture optotype acuity tests are under development.[6,7] Allen figures, Lighthouse characters, and the Sail Boat Chart are not standardized and are no longer recommended for use, nor are the Tumbling E or Landolt C charts, because a child of preschool age may not yet have developed the ability to express the orientation of these optotypes. HOTV symbols are easier for the young child to understand, as they are symmetric and not subject to letter reversal. With the examiner pointing to a symbol with a finger under it, a timid child can point to the optotypes that he or she recognizes on a card with similar symbols; this allows the child to effectively offer nonverbal responses during testing. Once a child can distinguish letters, a chart with letter optotypes should be used. Although the traditional Snellen chart remains in wide usage, Sloan letter charts present letters in a standardized fashion and should be used for acuity testing if they are available.

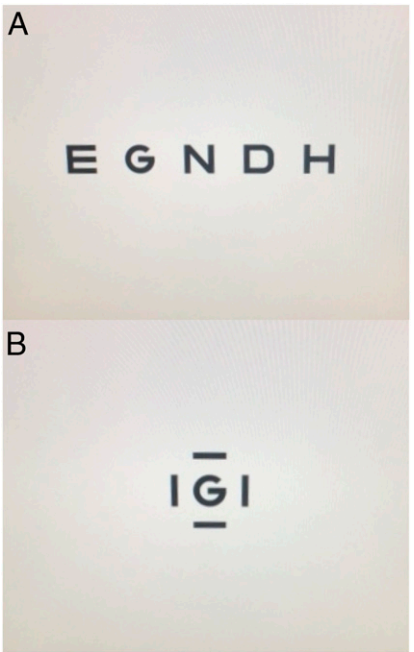

FIGURE 2
A, Five 20/50 letters presented in a row. B, Crowding bars isolate a single letter on the same 20/50 line, making it easier for a child to identify the letter, but are less subject to the "crowding phenomenon" (see text).

Screening Process

Large optotypes at the top of an eye chart or on handheld cards are first reviewed with the child with both eyes open to help the child understand the test. After this review, 1 eye is occluded (preferably by an occlusive patch or tape) and lines of optotypes or cards with single crowded optotypes (ie, the figure is surrounded by bars on all 4 sides) are presented to each eye separately. Effective occlusion, such as with tape or an occlusive patch of the eye not being tested, is important to eliminate the possibility of peeking.

Threshold Line Evaluation

The time-honored method of testing visual acuity has been to ask the child to start at the top of an eye chart and continue reading down each line until he or she recites the smallest line of optotypes discernable with each eye tested separately. This method is called "threshold" acuity testing and remains a common method of acuity testing. It enables one to identify the best level of visual acuity in each eye. Thus, children with near-normal acuity who still have a mild difference in acuity between each eye can be detected. However, threshold line evaluation can be sufficiently time-consuming to result in loss of attention from a young subject.

Critical Line Evaluation

Young children, even those with normal vision, are frequently unable to attend sufficiently to small optotypes and identify them. "Critical line" screening is an effective alternative to threshold testing for identifying children with potentially serious vision concerns and can be more quickly administered than can screening by using threshold testing. The "critical line" is the age-dependent line a child is expected to see normally and pass. For screening purposes, it is unnecessary to measure acuity below the age-specific critical line to pass the test. The critical line to pass screening becomes smaller as age increases. Most eye charts present 4 to 6 optotypes per line, and passing the screening requires the child to correctly answer a simple majority of the optotypes present on the critical line appropriate for his or her age as follows:

- Ages 36 through 47 months: If attempted at this age, the critical line to pass screening is the 20/50 line
- Ages 48 through 59 months: The critical line to pass screening is the 20/40 line
- Ages 60 months and older: The critical line to pass screening is the 20/30 line (or the 20/32 line on some charts)

Establishing an Effective Screening Environment and Methodology

It is important that the screening area be conducive for assessing visual acuity and that proper technique is used to promote accurate screening. It is important that screening personnel be trained to recognize and avoid pitfalls that reduce the accuracy of visual acuity screening. Accurate screening of visual acuity requires dedicated and skilled staff members.

1. A well-illuminated area free from distraction is important. A quiet examination room or hallway is generally sufficient for this purpose.
2. An appropriate testing distance must be used. For children up to 5 years of age, especially when pictorial optotypes are used, this distance should be set at 10 feet rather than 20 feet as a standard. This shorter distance helps to enhance interaction between the child and the individual administering the screening without decreasing the accuracy of screening results. Indeed, current standardized preschool eye charts are typically calibrated for use at 10 feet. For children 6 years and older for whom a letter chart is used, the test distance may be appropriately set at either 10 feet or at the common standard of 20 feet, as long as the chart is properly calibrated for use at that distance.

   Increasingly, screening methods using short testing distances are becoming available in the form of handheld optotypes used at a testing distance of 5 feet[8] or as computer, tablet, or smart phone–based models with testing distances within 1 to 2 feet. Although the accuracy of screening visual acuity at these shorter distances has not yet been validated in large population-based studies, the use of these methods can fit well into small clinical work areas. One computer-based application, available from the Jaeb Center for Health Research, is specifically for use by nonophthalmic health care professionals. The Jaeb Visual Acuity Screener incorporates all current screening guidelines and is available free of charge for download and unlimited use at http://pedig.jaeb.org/JVAS.aspx.

3. It is important to recognize that children with visual impairment may inaccurately pass a vision screening if they peek around an incompletely covered eye or if they are able to correctly guess when only 2 or 3 optotype choices are presented. Use of an adhesive patch over the nontested eye is recommended. Visually impaired children may become uncooperative during an examination; such behavior should be considered a possible indicator of poor visual function.
4. The use of validated and standardized optotypes and acuity charts is important for an accurate assessment of vision. For this reason, only the LEA symbols and HOTV characters are recommended for preschool vision screening at this time. Other optotypes are not well validated in the screening environment.
5. Every effort should be made not to isolate shapes or letters inadvertently on a line with a finger or cover to "help" a struggling child. If performed in this manner, the visual acuity result may be made falsely elevated by blocking out the natural crowding inherent in open lines of letters. If single optotypes are presented, they should include "crowding bars."
6. Screening visual acuity to the child's threshold (ie, best possible acuity) may provide a less accurate result than testing to the age-appropriate critical line for that child. Critical line testing is an appropriate alternative to threshold testing, requires less time to administer, and may provide a more accurate screening assessment of a child's visual function.

Incorporating these concepts into clinical practice offers a quick and reliable assessment of visual acuity in young children. To assist pediatricians and primary care physicians, the American Association for Pediatric Ophthalmology and Strabismus has developed a Vision Screening Kit designed specifically for young children that incorporates these important concepts. It is available commercially and can be purchased from the AAP.

For healthy children 6 years and older, testing of visual acuity using optotype-based vision charts at 10 or

20 feet remains the preferred method for screening and should be repeated every 1 to 2 years (Table 1).

Although barriers to its use exist, a level-1 Current Procedural Terminology (CPT) code, 99173, has been established for visual acuity screening and is available to primary care physicians to seek payment for this testing.

INSTRUMENT-BASED SCREENING TECHNIQUES

Instrument-based screening is endorsed by the AAP[2] and by the US Preventive Services Task Force as a

TABLE 1 Eye Examination Guidelines

Function	Recommended Tests	Referral Criteria	Comments
		Newborn to 6 mo	
Vision assessment	Fixation and follow response	Inconsistent or no response by 3 mo	
Ocular media clarity	Red reflex	White, pupil, dark spots, absent or asymmetric reflex	
External inspection	Direct observation	Any ocular abnormality of concern	
		6 to 12 mo	
Pupil examination	Flashlight	As above for ages newborn to 6 mo, plus	
		Ages 1–3 y	
		As above for ages 6 mo to 12 mo, plus	
Instrument-based vision screening when available (CPT 99174)	Photoscreening Autorefraction	Failed screening as indicated by the device	
Distance visual acuity may be attempted at age 3 y	HOTV or LEA Symbols	Fewer than a simple majority of optotypes correct on the 10/25 (20/50) line with either eye tested monocularly at 10 ft	
		Ages 4–5 y	
Distance visual acuity or instrument-based screening when available (CPT 99173)	HOTV or LEA symbols	A simple majority of figures correct on the age-appropriate critical line with either eye tested monocularly at 10 ft	1. Use a well-illuminated area free from distraction. 2. Either critical line testing or threshold testing may be used (see text for details). 3. Testing distance of 10 ft is recommended for all visual acuity tests. 4. A line of figures is preferred over single figures, unless the single figures are "crowded" (see text). 5. The fellow eye should be covered by an occluder held by the examiner or by an adhesive occluder patch applied to the eye; the examiner should determine that it is not possible to peek with the nontested eye.
		Ages: **48–59 mo:** 10/20 (=20/40) **60+ mo:** 10/15 (=20/30) or For threshold testing only: a 2-line difference between eyes, even with the passing range; eg, 20/15 (20/30) and 10/10 (20/20) for a 60-mo-old	
Ocular alignment	Cross cover test	Any eye movement	Child must be fixing on a target while cross cover test is performed.
Any asymmetry of pupil color, size, brightness			Direct ophthalmoscope used to view both red reflexes simultaneously in a darkened room from 2–3 feet away; detects asymmetric refractive errors as well.
Ocular media clarity	Red reflex	White pupil, dark spots in pupil, absent red reflex	Direct ophthalmoscope, darkened room. View each red reflex separately at 12–18 inches; white reflex indicates possible retinoblastoma. Dark or absent reflex indicates possible cataract.

TABLE 1 Continued

Function	Recommended Tests	Referral Criteria	Comments
		Ages ≥6 y	
Distance visual acuity; instrument-based screening when available for children unable to perform acuity	Sloan letters or Snellen letters HOTV or LEA symbols	Fewer than a simple majority of optotypes correct on the 10/15 (20/30) line with either eye tested monocularly at 10 ft	1. Tests are listed in decreasing order of cognitive difficulty; the highest test that the child is capable of performing should be used. 2. Use a well-illuminated area free from distraction. 3. Either critical line testing or threshold testing may be used (see text for details). 4. Testing distance of 10 ft is recommended for all visual acuity tests. 5. A line of figures is preferred over single figures unless the single figures are "crowded" (see text). 6. The fellow eye should be covered by an occluder held by the examiner or by an adhesive occluder patch applied to the eye; the examiner should determine that it is not possible to peek out of the covered eye.
		or	
		For threshold testing: only: a 2-line difference between eyes, even within the passing range; eg, 10/10 (20/20) and 10/15 (20/30)	
		Any eye movement	Simultaneous red reflex test (Bruckner test). Child must be fixing on a target while cross cover test is performed.
Ocular media clarity	Red reflex	White pupil, dark spots, absent reflex	Direct ophthalmoscope, darkened room. View each red reflex separately at 12–18 inches; white reflex indicates possible retinoblastoma. Dark or absent reflex indicates possible cataract.

valid method for screening very young children.[9] A recent randomized, controlled, multicentered crossover study demonstrated photoscreening to be superior to direct testing of visual acuity for screening well children ages 3 to 6 years in the pediatric office.[10] If available, instrument-based screening can be attempted beginning at age 12 months,[11] and a previous study has demonstrated better eventual outcomes for children undergoing their first photoscreening before 2 years of age.[12]

Instrument-based screening can be relatively quick and requires less attention from the child compared with traditional visual acuity screening. Screening instruments identify optical and physical characteristics that indicate the presence of ocular conditions known to cause amblyopia. Similar to the code for visual acuity screening, a level-1 CPT code, 99174, has been assigned to photoscreening and enables the primary care physician to seek payment for its use. CPT codes 99173 and 99174 are specific for visual acuity screening and photoscreening, respectively.

Two types of instrument-based vision screening are now available for use in ambulatory care settings. Although neither type provides a direct assessment of visual acuity, both identify ocular risk factors that can lead to early vision loss in children. Once children can read an eye chart easily, optotype-based acuity should supplement instrument-based testing. The actual age for this is not yet well established and likely varies depending on the child.

The most common ocular abnormalities seen during the early childhood years are strabismus, anisometropia, and a high magnitude of uncorrected refractive errors: hypermetropia, myopia, and astigmatism. The American Association for Pediatric Ophthalmology and Strabismus has developed refractive criteria to help

TABLE 2 Amblyopia Risk Factor Targets Recommended by the American Association for Pediatric Ophthalmology and Strabismus

	Refractive Risk Factor Targets			
Age, mo	Astigmatism, D	Hyperopia, D	Anisometropia, D	Myopia, D
12–30	>2.0	>4.5	>2.5	>−3.5
31–48	>2.0	>4.5	>2.0	>−3.0
>48	>1.5	>3.0	>1.5	>−1.5
	Nonrefractive Risk Factor Targets			
All ages	Media opacity >1 mm Manifest strabismus >8 prism D in primary position			

D, diopters

From Donahue et al.[13]

primary care physicians appreciate the levels of refractive error known to increase risk of amblyopia (Table 2).[13] Referral criteria that best detect these amblyopia risk factors may vary depending on the screening instrument used and the desired levels of sensitivity and specificity.

Photoscreening devices identify optical characteristics of the eyes to estimate refractive error, media clarity, ocular alignment, and eyelid position. Abnormalities in these characteristics constitute risk factors for the presence or development of amblyopia. Photoscreening has been shown to have high sensitivity and specificity in community and office settings.[14–20] Photoscreening instruments assess both eyes simultaneously and the images can be interpreted by trained operators, by a central reading center, or with computer software.

Autorefraction instruments, like photoscreeners, also are useful for screening young children.[21,22] Handheld autorefractors use optical methods to estimate the refractive error of each eye, 1 eye at a time, and as such, are limited in their ability to detect strabismus in the absence of an abnormal refractive error. However, autorefractors remain useful in detecting anisometropia in the absence of strabismus, which is the most common cause of amblyopia undetected at an early age.

Instrument-based devices using technology based on visual evoked potentials[23] and retinal birefringence[24] are currently in development and may provide additional means to assess visual acuity and ocular health in young children.

For all instrument-based devices, the sensitivity and specificity to detect an ocular abnormality has been carefully considered by their manufacturers. Typically, when a high sensitivity (ie, high rate of detection of at-risk children) is chosen, an increase in overreferrals (ie, low specificity) results. Conversely, when a high specificity is set, there is often a low sensitivity (ie, reduced detection of at-risk children). Given these factors, the referral criteria can be adjusted for many instruments on the basis of the child's age and desired levels of sensitivity and specificity.

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ABBREVIATIONS

AAP: American Academy of Pediatrics
CPT: Current Procedural Terminology

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JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Vision Screening in Children Aged 6 Months to 5 Years
US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

IMPORTANCE One of the most important causes of vision abnormalities in children is amblyopia (also known as "lazy eye"). Amblyopia is an alteration in the visual neural pathway in a child's developing brain that can lead to permanent vision loss in the affected eye. Among children younger than 6 years, 1% to 6% have amblyopia or its risk factors (strabismus, anisometropia, or both). Early identification of vision abnormalities could prevent the development of amblyopia.

SUBPOPULATION CONSIDERATIONS Studies show that screening rates among children vary by race/ethnicity and family income. Data based on parent reports from 2009-2010 indicated identical screening rates among black non-Hispanic children and white non-Hispanic children (80.7%); however, Hispanic children were less likely than non-Hispanic children to report vision screening (69.8%). Children whose families earned 200% or more above the federal poverty level were more likely to report vision screening than families with lower incomes.

OBJECTIVE To update the 2011 US Preventive Services Task Force (USPSTF) recommendation on screening for amblyopia and its risk factors in children.

EVIDENCE REVIEW The USPSTF reviewed the evidence on the accuracy of vision screening tests and the benefits and harms of vision screening and treatment. Surgical interventions were considered to be out of scope for this review.

FINDINGS Treatment of amblyopia is associated with moderate improvements in visual acuity in children aged 3 to 5 years, which are likely to result in permanent improvements in vision throughout life. The USPSTF concluded that the benefits are moderate because untreated amblyopia results in permanent, uncorrectable vision loss, and the benefits of screening and treatment potentially can be experienced over a child's lifetime. The USPSTF found adequate evidence to bound the potential harms of treatment (ie, higher false-positive rates in low-prevalence populations) as small. Therefore, the USPSTF concluded with moderate certainty that the overall net benefit is moderate for children aged 3 to 5 years.

CONCLUSIONS AND RECOMMENDATIONS The USPSTF recommends vision screening at least once in all children aged 3 to 5 years to detect amblyopia or its risk factors. (B recommendation) The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of vision screening in children younger than 3 years. (I statement)

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Author/Group Information: The US Preventive Services Task Force (USPSTF) members are listed at the end of this article.

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Severe Exfoliating Skin Conditions

Plain Language Summary:

Coverage question: Should OHP cover severe shedding of the skin that can affect overall health?

Should OHP cover this treatment? Yes, based on expert input.

Coverage Question: Should multiple diagnosis codes currently on the uncovered erythematous conditions line that represent severe exfoliating skin conditions be moved to a covered line?

Question source: HERC staff

Background: During the revisions to the breast reduction for macromastia topic, staff reviewed line 504 ERYTHEMATOUS CONDITIONS and determined that some diagnoses on that line are serious and require medical treatment. ICD-10-CM L30.4 (Erythema intertrigo) was added to line 426 SEVERE INFLAMMATORY SKIN DISEASE as part of the breast reduction for macromastia review.

One diagnosis on line 504 is ICD-10-CM L26 (Exfoliative dermatitis). Generalized exfoliative dermatitis, or erythroderma, is a severe inflammation of the entire skin surface. This is due to a reaction to certain medicines, a pre-existing skin condition, and sometimes cancer. In approximately 25% of people, there is no identifiable cause. It is characterized by redness and scaling of the skin that begins in patches and spreads. The skin begins to slough off. This leads to problems with temperature regulation, protein and fluid loss, as well as an increased metabolic rate. Treatment is stopping any offending medications, oral steroids for severe cases, rehydration, and comprehensive wound care to prevent infection. This condition frequently requires hospitalization and can be fatal. Erythroderma is coded with either ICD-10-CM L26, L53.8 (Other specified erythematous conditions) or L53.9 (Erythematous condition, unspecified). If caused by cancer, it may be coded with L54 (Erythema in diseases classified elsewhere). All of these diagnoses are on line 504.

Additionally, the ICD-10-CM L49 series (Exfoliation due to erythematous condition) is on line 504. ICD-10-CM L49.1 is <10% of body surface area, but the percent of body surface area increases up to >90% with ICD-10-CM L49.9. Similar burn diagnoses are on line 605 MINOR BURNS (<10% BSA), line 127 MODERATE BURNS (larger surface area or greater depth of burn) or line 57 SEVERE BURNS (highest surface area with greatest depth of burn). Erythoderma would be present if the exfoliation was over 75% of the body surface area (ICD-10-CM codes L49.7-L49.9).

Previous HSC/HERC reviews:
Line 504 was included in the “below the line” review done by HERC staff last year.

Severe Exfoliating Skin Conditions

Current Prioritized List/Coverage status:

Line 504 ERYTHEMATOUS CONDITIONS

ICD-10 Code	Code Description
L26	Exfoliative dermatitis
L49.1	Exfoliation due to erythematous condition involving less than 10 percent of body surface
L49.2	20-29 percent of BSA
L49.3	30-39 percent of BSA
L49.4	40-49 percent of BSA
L49.5	50-59 percent of BSA
L49.6	60-69 percent of BSA
L49.7	70-79 percent of BSA
L49.8	80-89 percent of BSA
L49.9	90 percent or more of BSA
L53.8	Other specified erythematous conditions
L53.9	Erythematous condition, unspecified
L54	Erythema in diseases classified elsewhere

GUIDELINE NOTE 21, SEVERE INFLAMMATORY SKIN DISEASE

Lines 426,482,504,533,542,555,656

Inflammatory skin conditions included in this guideline are:

A) Psoriasis
B) Atopic dermatitis
C) Lichen planus
D) Darier disease
E) Pityriasis rubra pilaris
F) Discoid lupus
G) Vitiligo
H) Prurigo nodularis

The conditions above are included on Line 426 if severe, defined as having functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's Dermatology Life Quality Index (CDLQI) ≥ 13 (or severe score on other validated tool) AND one or more of the following:

A) At least 10% of body surface area involved
B) Hand, foot, face, or mucous membrane involvement.

Otherwise, these conditions above are included on Lines 482, 504, 533, 542, 555 and 656.

For severe psoriasis, treatments included on this line are topical agents, phototherapy, targeted immune modulator medications and other systemic medications.

For severe atopic dermatitis/eczema, treatments included on this line are topical moderate- to high-potency corticosteroids, topical calcineurin inhibitors (for example, tacrolimus), narrowband UVB, and

oral immunomodulatory therapy (e.g. cyclosporine, methotrexate, or oral corticosteroids). Targeted immune modulators (for example, dupilumab) are included on this line when:

A) Prescribed in consultation with a dermatologist or allergist or immunologist, AND

B) The patient has failed (defined as inadequate efficacy, intolerable side effects, or side effects that pose a health risk) a 4 week trial of a combination of topical moderate to high potency topical steroids and a topical non-steroidal agent OR an oral immunomodulator.

JAK inhibitor (for example, upadacitinib or abrocitinib) therapy is included on this line when other immunomodulatory therapy has failed to adequately control disease (defined as inadequate efficacy, intolerable side effects, or side effects that pose a health risk).

ICD-10-CM Q82.8 (Other specified congenital malformations of skin) is included on Line 426 only for Darier disease.

Expert input:

Dr. Sarah Leitenberger, OHSU dermatology

> …erythroderma is a severe condition with major implications to systemic health. When acute, it can require hospitalization for fluid/electrolyte balance and acute cardiovascular reasons. When chronic, there are impacts on nutrition, growth and chronic cardiovascular health.
>
> Fortuitously, this ties in directly with our request to reconsider "ichthyosis". Severe ichthyosis such as Harlequin ichthyosis, lamellar ichthyosis and non-bullous congenital ichthyosiform erythroderma all involve exfoliation of >75% BSA.

Severe Exfoliating Skin Conditions

HERC staff summary:

Several severe exfoliating skin conditions currently in the unfunded region of the Prioritized List should be added to line 426 and the inflammatory skin disease guideline should be modified to indicate when these conditions are on the covered line.

HERC staff recommendations:

1) Add the following ICD-10-CM codes to line 426 SEVERE INFLAMMATORY SKIN DISEASE and keep on line 504 ERYTHEMATOUS CONDITIONS

ICD-10 Code	**Code Description**
L26	Exfoliative dermatitis
L49.7	Exfoliation due to erythematous condition involving 70-79 percent of body surface
L49.8	80-89 percent of BSA
L49.9	90 percent or more of BSA
L53.8	Other specified erythematous conditions
L53.9	Erythematous condition, unspecified
L54	Erythema in diseases classified elsewhere

2) Modify GN21 as shown below
    a. Suggested wording from another issue is shown in purple

GUIDELINE NOTE 21, SEVERE INFLAMMATORY SKIN DISEASE

Lines 426,482,504,533,542,555,656

Inflammatory skin conditions included in this guideline are:

A) Psoriasis
B) Atopic dermatitis
C) Lichen planus
D) Darier disease
E) Pityriasis rubra pilaris
F) Discoid lupus
G) Vitiligo
H) Prurigo nodularis
I) Erythema intertrigo

The conditions above are included on Line 426 if severe, defined as having functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's Dermatology Life Quality Index (CDLQI) ≥ 13 (or severe score on other validated tool) AND one or more of the following:

C) At least 10% of body surface area involved
D) Hand, foot, face, or mucous membrane involvement.

Otherwise, these conditions above are included on Lines 482, 504, 533, 542, 555 and 656.

For severe psoriasis, treatments included on this line are topical agents, phototherapy, targeted immune modulator medications and other systemic medications.

Severe Exfoliating Skin Conditions

For severe atopic dermatitis/eczema, treatments included on this line are topical moderate- to high-potency corticosteroids, topical calcineurin inhibitors (for example, tacrolimus), narrowband UVB, and oral immunomodulatory therapy (e.g. cyclosporine, methotrexate, or oral corticosteroids). Targeted immune modulators (for example, dupilumab) are included on this line when:

A) Prescribed in consultation with a dermatologist or allergist or immunologist, AND

B) The patient has failed (defined as inadequate efficacy, intolerable side effects, or side effects that pose a health risk) a 4 week trial of a combination of topical moderate to high potency topical steroids and a topical non-steroidal agent OR an oral immunomodulator.

JAK inhibitor (for example, upadacitinib or abrocitinib) therapy is included on this line when other immunomodulatory therapy has failed to adequately control disease (defined as inadequate efficacy, intolerable side effects, or side effects that pose a health risk).

ICD-10-CM Q82.8 (Other specified congenital malformations of skin) is included on Line 426 only for Darier disease.

ICD-10-CM L26 (Exfoliative dermatitis), L49.7-L49.9 (Exfoliation due to erythematous condition involving 70% to >90% of body surface), L53.8 (Other specified erythematous conditions), L53.9 (Erythematous condition, unspecified), and L54 (Erythema in diseases classified elsewhere) are included on line 426 only when representing erythroderma or when the exfoliation extends over 75% of body surface area. Otherwise, these diagnoses are included on line 504.

Refugee Screening

Plain Language Summary:

Coverage question: Should OHP cover medical screenings for people arriving from other countries who are seeking safety and protection from war or other dangers?

Should OHP cover this treatment? Yes, this screening is a federal requirement.

Coverage Question: Should a new diagnosis code be added to the preventive services line to represent refugee screening?

Question source: Multnomah County Health Department, DHS Refugee Policy Unit, HSD

Background: Programs that provide resettlement services on behalf of the federal government must provide refugee domestic screening. This screening involves a history and physical, screening for various parasites, STIs, and viruses, assessing nutrition and growth, assessing mental health, and providing necessary immunizations.

The CDC has protocols in place for refugee screening, available at https://www.cdc.gov/immigrantrefugeehealth/guidelines/refugee-guidelines.html

Multnomah County Health Department has been receiving multiple denials of claims for refugee screening exams. Providers are using a variety of diagnosis codes, including ICD-10-CM Z02.89 (Encounter for administrative examinations, unspecified) and Z76.89 (Persons encountering health services in other specified circumstances) which are currently informational only.

OHA staff and the refugee screening programs have met and are requesting that ICD-10-CM Z65.5 (Exposure to disaster, war and other hostilities) be added to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS to designate an encounter as refugee screening. This will allow OHA and providers to identify encounters that are part of this program. Line 3 has all of the screening, immunization and exam CPT codes required for this type of screening. Normal preventive exam or office visit codes will not allow identification that these exams were done as part of the federal program.

Current Prioritized List/Coverage status:

ICD-10-CM Z65.5 (Exposure to disaster, war and other hostilities) is currently on the INFORMATIONAL DIAGNOSES file

HERC staff summary:

In order to comply with federally mandated refugee screening, OHA and the refugee screening programs need a unique diagnosis code to identify claims related to refugee screening. Adding the requested code to line 3 will allow all the required screening activities to pair and be reimbursed.

Refugee Screening

HERC staff recommendation:

1) Add ICD-10-CM Z65.5 (Exposure to disaster, war and other hostilities) to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
    a. Advise HSD to remove ICD-10-CM Z65.5 from the INFORMATIONAL DIAGNOSES file